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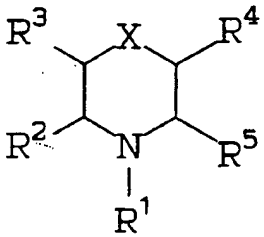
(54) Title: MORPHOLINE AND THIOMORPHOLINE TACHYKININ RECEPTOR ANTAGONISTS



(I)

(57) Abstract

Substituted heterocycles of general structural formula (I) are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, and asthma and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.

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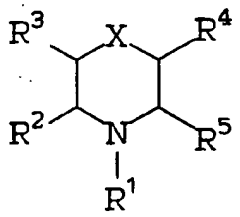
TITLE OF THE INVENTION

MORPHOLINE AND THIOMORPHOLINE TACHYKININ RECEPTOR ANTAGONISTS

SUMMARY OF THE INVENTION

This application is a continuation-in-part of copending application Serial No. 07/971,448, filed November 4, 1992, which is a continuation-in-part of copending application Serial No. 07/905,976, filed June 29, 1992.

This invention is concerned with novel compounds represented by structural formula I:



I

wherein R^1, R^2, R^3, R^4, R^5, and X are hereinafter defined.

The invention is also concerned with pharmaceutical formulations comprising these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain disorders.

The compounds of this invention are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases, pain or migraine and asthma.

Also, some of these compounds are calcium channel blockers and are useful in the treatment of cardiovascular disorders such as angina, hypertension or ischemia.

BACKGROUND OF THE INVENTION

Analgesia has historically been achieved in the central nervous system by opiates and analogs which are addictive, and peripherally by cyclooxygenase inhibitors that have gastric side effects. Substance P antagonists may induce analgesia both centrally and peripherally. In addition, substance P antagonists are inhibitory of neurogenic inflammation.

The neuropeptide receptors for substance P (neurokinin-1; NK-1) are widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes. This includes sensory perception of olfaction, vision, audition and pain,

movement control, gastric motility, vasodilation, salivation, and micturition (B. Pernow, Pharmacol. Rev., 1983, 35, 85-141). The NK1 and NK2 receptor subtypes are implicated in synaptic transmission (Laneuville et al., Life Sci., 42: 1295-1305 (1988)).

The receptor for substance P is a member of the superfamily of G protein-coupled receptors. This superfamily is an extremely diverse group of receptors in terms of activating ligands and biological functions. In addition to the tachykinin receptors, this receptor superfamily includes the opsins, the adrenergic receptors, the muscarinic receptors, the dopamine receptors, the serotonin receptors, a thyroid-stimulating hormone receptor, a luteinizing hormone-choriogonadotropic hormone receptor, the product of the oncogene ras, the yeast mating factor receptors, a Dictyostelium cAMP receptor, and receptors for other hormones and neurotransmitters (see A.D. Hershey, et al., J. Biol. Chem., 1991, 226, 4366-4373).

Substance P (also called "SP" herein) is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The tachykinins are distinguished by a conserved carboxyl-terminal sequence Phe-X-Gly-Leu-Met-NH_2. In addition to SP the known mammalian tachykinins include neurokinin A and neurokinin B. The current nonmenclature designates the receptors for SP, neurokinin A, and neurokinin B as NK-1, NK-2, and NK-3, respectively.

More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals and possesses a characteristic amino acid sequence that is illustrated below:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2 (Chang et al., Nature New Biol. 232, 86 (1971); D.F. Veber et al., U.S. Patent No. 4,680,283).

Neurokinin A possesses the following amino acid sequence:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2.

Neurokinin B possesses the following amino acid sequence:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2.

Substance P acts as a vasodilator, a depressant, stimulates salivation and produces increased capillary permeability. It is also capable of producing both analgesia and hyperalgesia in animals, depending on dose and pain responsiveness of the animal (see R.C.A. Frederickson et al., Science, 199, 1359 (1978); P. Oehme et al., Science, 208, 305 (1980)) and plays a role in sensory transmission and pain perception (T.M. Jessell, Advan. Biochem. Psychopharmacol. 28, 189 (1981)). For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510]. In particular, substance P has been shown to be involved

in the transmission of pain in migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), and in arthritis (Levine et al. Science, (1984) 226 547-549). These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease, ulcerative colitis and Crohn's disease, etc. (see Mantyh et al., Neuroscience, 25 (3), 817-37 (1988) and D. Regoli in "Trends in Cluster Headache" Ed. F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, 1987, pp. 85-95).

It is also hypothesized that there is a neurogenic mechanism for arthritis in which substance P may play a role (Kidd et al., "A Neurogenic Mechanism for Symmetric Arthritis" in The Lancet, 11 November 1989 and Gronblad et al., "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10). Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis (O'Byrne et al., in Arthritis and Rheumatism (1990) 33 1023-8). Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions (Hamelet et al., Can. J. Pharmacol. Physiol. (1988) 66 1361-7), immunoregulation (Lotz et al., Science (1988) 241 1218-21, Kimball et al., J. Immunol. (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or neuronal control of the viscera (Mantyh et al., PNAS (1988) 85

3235-9) and, possibly by arresting or slowing β-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press]. Antagonists selective for the neurokinin-1 (NK-1) and/or the neurokinin-2 (NK-2) receptor may be useful in the treatment of asthmatic disease (Frossard et al., Life Sci., 49, 1941-1953 (1991); Advenier, et al., Biochem. Biophys. Res. Comm., 184(3), 1418-1424 (1992)).

Substance P antagonists may be useful in mediating neurogenic mucus secretion in mammalian airways and hence provide treatment and symptomatic relief in diseases characterized by mucus secretion, in particular, cystic fibrosis [S. Ramnarine, et al., abstract to be presented at 1993 ALA/ATS Int'l Conference, 16-19 May, 1993, to be published in Am. Rev. of Respiratory Dis., May 1993, in press].

In the recent past, some attempts have been made to provide peptide-like substances that are antagonists for substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases listed above. See for example European patent applications (EPO Publication Nos. 0,347,802, 0,401,177 and 0,412,452) which disclose various peptides as neurokinin A antagonists. Similarly, EPO Publication No. 0,336,230 discloses

heptapeptides which are substance P antagonists useful in the treatment of asthma. Merck U.S. Patent No. 4,680,283 also discloses peptidal analogs of substance P.

Certain inhibitors of tachykinins have been described in U.S. Patent No. 4,501,733, by replacing residues in substance P sequence by Trp residues.

A further class of tachykinin receptor antagonists, comprising a monomeric or dimeric hexa- or heptapeptide unit in linear or cyclic form, is described in GB-A-2216529.

The peptide-like nature of such substances make them too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, as they are expected to be more stable from a metabolic point of view than the previously-discussed agents.

It is known in the art that baclofen (ß-(aminoethyl)-4-chlorobenzenepropanoic acid) in the central nervous system effectively blocks the excitatory activity of substance P, but because in many areas the excitatory responses to other compounds such as acetylcholine and glutamate are inhibited as well, baclofen is not considered a specific substance P antagonist. Pfizer WIPO patent applications (PCT Publication Nos. WO 90/05525, WO 90/05729, WO 91/18899, WO 92/12151 and WO 92/12152) and publications (Science, 251, 435-437 (1991); Science, 251, 437-439 (1991); J. Med. Chem., 35,

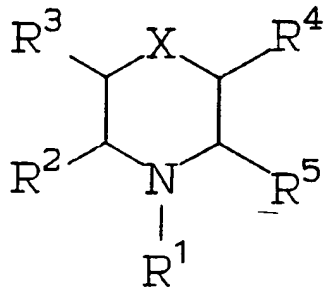
2591-2600 (1992)) disclose 2-arylmethyl-3-substituted amino-quinuclidine derivatives which are disclosed as being useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. A Glaxo European patent application (EPO Publication No. 0.360.390) discloses various spirolactam-substituted amino acids and peptides which are antagonists or agonists of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/06079) discloses fused-ring analogs of nitrogen-containing nonaromatic heterocycles as useful for the treatment of diseases mediated by an excess of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/15585 discloses 1-azabicyclo[3.2.2]nonan-3-amine derivatives as substance P antagonists. A Sanofi publication (Life Sci., 50, PL101-PL106 (1992)) discloses a 4-phenyl piperidine derivative as an antagonist of the neurokinin A (NK2) receptor.

Howson et al. (Biorg. & Med. Chem. Lett., 2 (6), 559-564 (1992)) disclose certain 3-amino and 3-oxy quinuclidine compounds and their binding to substance P receptors. EPO Publication 0.499.313 discloses certain 3-oxy and 3-thio azabicyclic compounds as tachykinin antagonists. U.S. Patent No. 3.506.673 discloses certain 3-hydroxy quinuclidine compounds as central nervous system stimulants. A Pfizer EPO Patent application (EPO Publication 0.436.334) discloses certain 3-aminopiperidine compounds as substance P antagonists. U.S. Patent No. 5.064.838 discloses certain 1,4-disubstituted

piperidinyl compounds as analgesics. PCT Publication No. WO 92/12128 discloses certain piperidine and pyrrolidine compounds as analgesics. Peyronel, et al. (Biorg & Med. Chem. Lett., 2 (1), 37-40 (1992)) disclose a fused ring pyrrolidine compound as a substance P antagonist. EPO Publication No. 0,360,390 discloses certain spirolactam derivatives as substance P antagonists. U.S. Patent No. 4,804,661 discloses certain piperazine compounds as analgesics. U.S. Patent No. 4,943,578 discloses certain piperazine compounds useful in the treatment of pain. PCT Publication No. WO 92/01679 discloses certain 1,4-disubstituted piperazines useful in the treatment of mental disorders in which a dopaminergic deficit is implicated.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by structural formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) hydrogen;

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl,

(iii) hydroxy-C_{1-6} alkyl, and

(iv) phenyl,

(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above,

(m) $-CO_2R^9$, wherein R^9 is as defined above;

(n) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,

(B) benzofuranyl,

(C) benzothiophenyl,

(D) benzoxazolyl,
(E) furanyl,
(F) imidazolyl,
(G) indolyl,
(H) isooxazolyl,
(I) isothiazolyl,
(J) oxadiazolyl,
(K) oxazolyl,
(L) pyrazinyl,
(M) pyrazolyl,
(N) pyridyl,
(O) pyrimidyl,
(P) pyrrolyl,
(Q) quinolyl,
(R) tetrazolyl,
(S) thiadiazolyl,
(T) thiazolyl,
(U) thienyl,
(V) triazolyl,
(W) azetidinyl,
(X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
(AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,
and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) hydroxy,
(v) thioxo,
(vi) $-SR^9$, wherein R^9 is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
(x) trifluoromethyl,
(xi) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and R^9 and R^{10} are as defined above,
(xii) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(xiii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(xiv) $-CO_2R^9$, wherein R^9 is as defined above, and
(xv) $-(CH_2)_m-OR^9$, wherein m and R^9 are as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above,
(k) heterocycle, wherein the heterocycle is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(n) $-COR^9$, wherein R^9 is as defined above;

(o) $-CO_2R^9$, wherein R^9 is as defined above;

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above, and

(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(n) $-COR^9$, wherein R^9 is as defined above;

(o) $-CO_2R^9$, wherein R^9 is as defined above;

and the groups R^1 and R^2 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,

(b) piperidinyl,

(c) pyrrolyl,

(d) pyridinyl,

(e) imidazolyl,

(f) oxazolyl, and

(g) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,

(ii) oxo,

(iii) C_{1-6}alkoxy,

(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(v) halo, and

(vi) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a carbocyclic ring selected from the group consisting of:

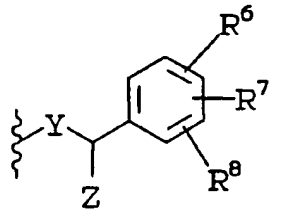
(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,
and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:
(i) C_{1-6}alkyl,
(ii) C_{1-6}alkoxy,
(iii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a heterocyclic ring selected from the group consisting of:
(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,
and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

X is selected from the group consisting of:
(1) -O-,
(2) -S-,
(3) -SO-, and
(4) $-SO_2-$;

R^4 is selected from the group consisting of:

(1) 

,

(2) $-Y-C_{1-8}$ alkyl, wherein the alkyl is unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,

(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) $-Y-C_{2-6}$ alkenyl, wherein the alkenyl is unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) -O(CO)-phenyl, wherein the phenyl is unsubstituted or substituted with one or more of R^6, R^7 and R^8;

R^5 is selected from the group consisting of:

(1) phenyl, unsubstituted or substituted with one or more of R^{11}, R^{12} and R^{13};

(2) C_{1-8} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
- (a) hydroxy,
- (b) oxo,
- (c) C_{1-6} alkoxy,
- (d) phenyl-C_{1-3} alkoxy,
- (e) phenyl,
- (f) -CN,
- (g) halo,
- (h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
- (i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
- (j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
- (k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
- (l) $-COR^9$, wherein R^9 is as defined above, and
- (m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
- (b) oxo,
- (c) C_{1-6} alkoxy,
- (d) phenyl-C_{1-3} alkoxy,

(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) heterocycle, wherein the heterocycle is as defined above;

R^6, R^7 and R^8 are independently selected from the group consisting of:
(1) hydrogen;
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,

(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(n) $-COR^9$, wherein R^9 is as defined above;

(o) $-CO_2R^9$, wherein R^9 is as defined above;

(6) halo,

(7) -CN,

(8) $-CF_3$,

(9) $-NO_2$,

(10) $-SR^{14}$, wherein R^{14} is hydrogen or C_{1-6}alkyl,

(11) $-SOR^{14}$, wherein R^{14} is as defined above,

(12) $-SO_2R^{14}$, wherein R^{14} is as defined above,

(13) NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,

(14) $CONR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(15) NR^9R^{10}, wherein R^9 and R^{10} are as defined above,

(16) $NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(17) hydroxy,

(18) C_{1-6}alkoxy,

(19) COR^9, wherein R^9 is as defined above,

(20) CO_2R^9, wherein R^9 is as defined above;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8;

Y is selected from the group consisting of:

(1) a single bond,
(2) -O-,
(3) -S-,
(4) -CO-,
(5) $-CH_2-$,
(6) $-CHR^{15}-$, and
(7) $-CR^{15}R^{16}-$, wherein R^{15} and R^{16} are independently selected from the group consisting of:
(a) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(i) hydroxy,
(ii) oxo,
(iii) C_{1-6} alkoxy,
(iv) phenyl-C_{1-3} alkoxy,
(v) phenyl,
(vi) -CN,
(vii) halo,
(viii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(ix) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(x) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(xi) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(xii) $-COR^9$, wherein R^9 is as defined above, and
(xiii) $-CO_2R^9$, wherein R^9 is as defined above;

(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(i) hydroxy,

(ii) C_{1-6} alkoxy,

(iii) C_{1-6} alkyl,

(iv) C_{2-5} alkenyl,

(v) halo,

(vi) -CN,

(vii) $-NO_2$,

(viii) $-CF_3$,

(ix) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,

(x) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(xi) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(xii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiii) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiv) $-COR^9$, wherein R^9 is as defined above, and

(xv) $-CO_2R^9$, wherein R^9 is as defined above;

Z is selected from:

(1) hydrogen,

(2) C_{1-4} alkyl, and

(3) hydroxy, with the proviso that if Y is -O-, Z is other than hydroxy,

or if Y is $-CHR^{15}-$, then Z and R^{15} may be joined together to form a double bond.

The compounds of the present invention have asymmetric centers and this invention includes all of the optical isomers and mixtures thereof.

In addition compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

When any variable (e.g., alkyl, aryl, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, etc.) occurs more than one time in any variable or in Formula I, its definition on each ocurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" includes those alkyl groups of a designated number of carbon atoms of either a straight, branched, or cyclic configuration. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso- sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, butoxy and pentoxy. "Alkenyl" is intended to include hydrocarbon chains of a specified number of carbon atoms of either a straight- or branched- configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, dimethylpentyl, and the like, and includes E and Z forms, where applicable. "Halogen" or "halo", as used herein, means fluoro, chloro, bromo and iodo.

The term "aryl" means phenyl or naphthyl either unsubstituted or substituted with one, two or three substituents selected from the group consisting of halo, C_{1-4}-alkyl, C_{1-4}-alkoxy, NO_2, CF_3, C_{1-4}-alkylthio, OH, $-N(R^6)_2$, $-CO_2R^6$, C_{1-4}-perfluoroalkyl, C_{3-6}-perfluorocycloalkyl, and tetrazol-5-yl.

The term "heteroaryl" means an unsubstituted, monosubstituted or disubstituted five or six membered aromatic heterocycle comprising from 1 to 3 heteroatoms selected from the group consisting of O, N and S and wherein the substituents are members selected from the group consisting of -OH, -SH, $-C_{1-4}$-alkyl, $-C_{1-4}$-alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2R^9$,$-N(R^9R^{10})$ and a fused benzo group;

As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, pamoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium.

In the compounds of formula I it is preferred that:

R^1 is selected from the group consisting of:

(1) C_{1-6} alkyl, substituted with one or more of the substituents selected from:

(a) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,
(B) imidazolyl,
(C) isooxazolyl,
(D) isothiazolyl,
(E) oxadiazolyl,
(F) pyrazinyl,
(G) pyrazolyl,
(H) pyridyl,
(I) pyrrolyl,
(J) tetrazolyl,
(K) thiadiazolyl,
(L) triazolyl, and
(M) piperidinyl,

and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) thioxo,
(v) cyano,
(vi) $-SCH_3$,
(vii) phenyl,

(viii) hydroxy,

(ix) trifluoromethyl,

(x) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and wherein R^9 and R^{10} are independently selected from:

(I) hydrogen,

(II) C_{1-6} alkyl,

(III) hydroxy-C_{1-6} alkyl, and

(IV) phenyl,

(xi) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above, and

(xii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above;

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl,

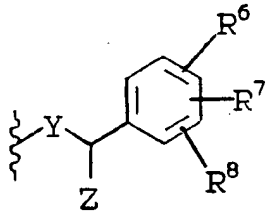
(3) C_{2-6} alkenyl, and

(4) phenyl;

X is -O-;

R^4 is:

(1)



,

R^5 is phenyl, unsubstituted or substituted with halo;

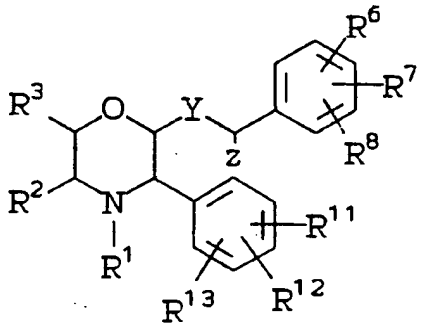
R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo, and
(4) $-CF_3$;

Y is -O-; and

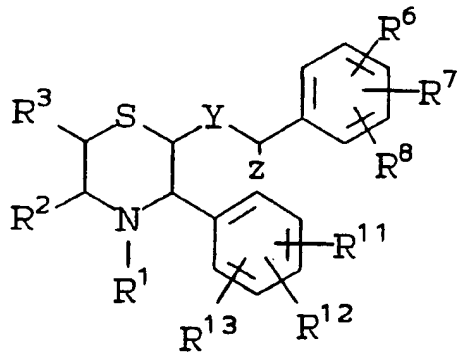
Z is hydrogen or C_{1-4} alkyl.

An embodiment of the novel compounds of this invention is that wherein X is O, R^4 is -YCHZ-phenyl, and R^5 is phenyl of structural formula:



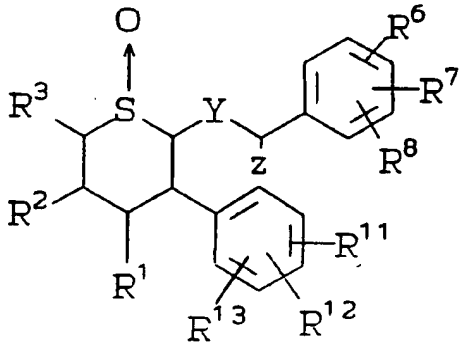
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined above.

Another embodiment of the novel compounds of this invention is that wherein X is S, R^4 is -Y-CHZ-phenyl, and R^5 is phenyl of structural formula:



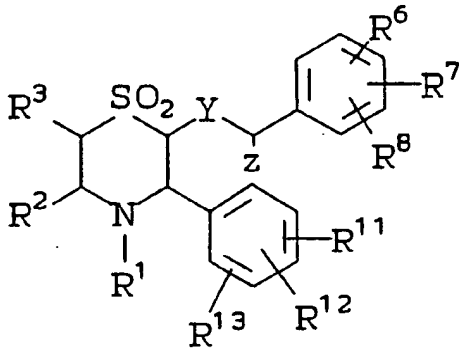
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined above.

Another embodiment of the novel compounds of this invention is that wherein X is SO, R^4 is -Y-CHZ-phenyl, and R^5 is phenyl of structural formula:



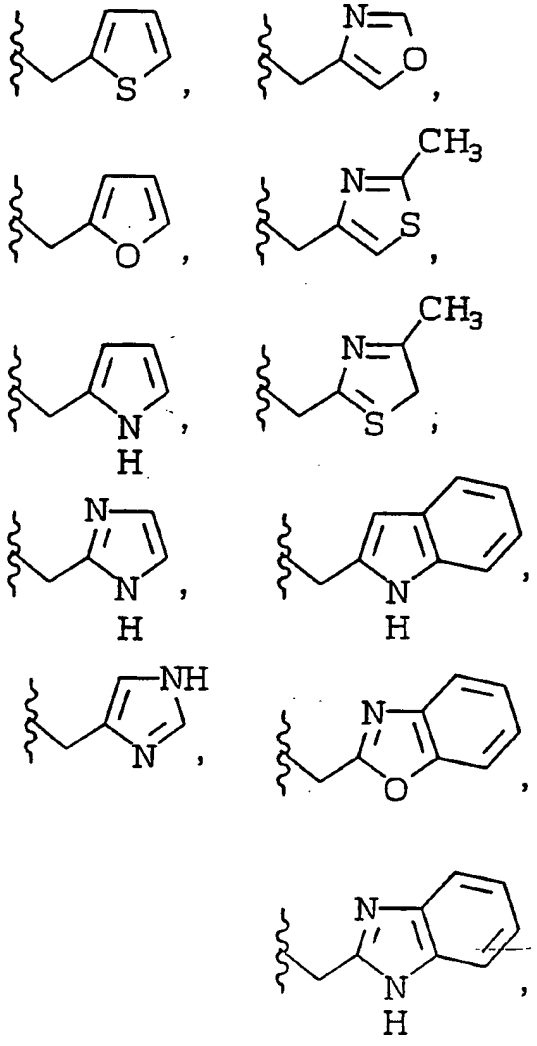
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined above.

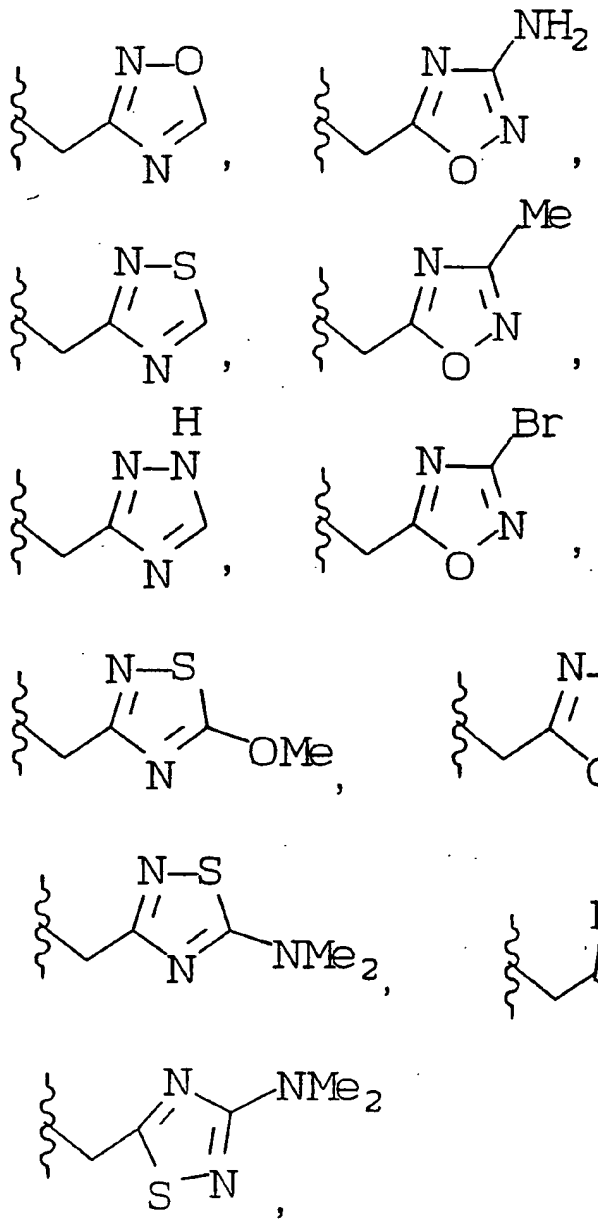
Another embodiment of the novel compounds of this invention is that wherein X is SO_2, R^4 is -Y-CHZ-phenyl, and R^5 is phenyl of structural formula:

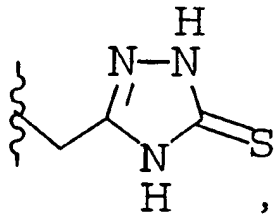
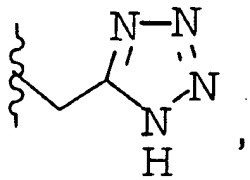
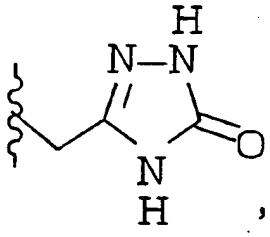
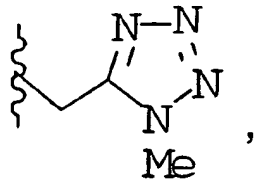
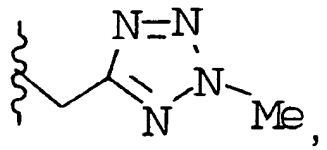
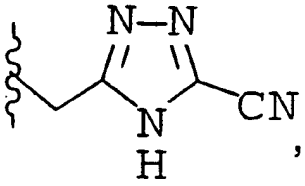
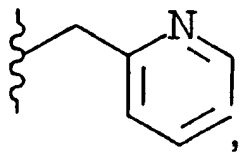
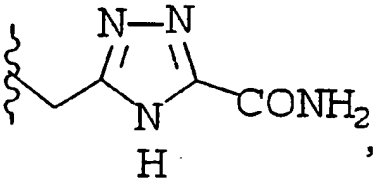
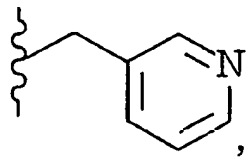
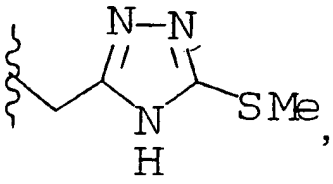
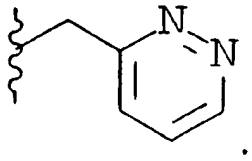


or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined above.

In the compounds of the present invention a preferred embodiment is that in which R^1 is selected from the following group of substituents:





Specific compounds within the scope of the present invention include:

1) (+/-)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

2) (2R,S)-(3,5-bis(trifluoromethyl)benzyloxy)-(3R)-phenyl-(6R)-methyl-morpholine;

3) (2R,S)-(3,5-bis(trifluoromethyl)benzyloxy)-(3S)-phenyl-(6R)-methyl-morpholine;

4) (+/-)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methylcarboxamido-morpholine;

5) (+/-)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methoxy-carbonylmethyl-morpholine;

6) 2-(2-(3,5-bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine;

7) 3-phenyl-2-(2-(3,5-bis(trifluoromethyl)phenyl)-ethyl)-morpholine;

8) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl-morpholine;

9) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl-morpholine;

10) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl-morpholine;

11) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl-morpholine;

12) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine;

13) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl-morpholine;

14) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine;

15) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl-morpholine;

16) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine;

17) 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

18) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

19) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl-morpholine;

20) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl-morpholine;

21) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;

22) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;

23) 2-(R)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine;

24) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine;

25) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-methyl-morpholine;

26) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine;

27) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine;

28) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine;

29) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine;

30) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

31) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;

32) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

33) 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

34) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

35) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

36) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

37) 4-(aminocarbonylmethyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

38) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

39) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

40) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;

41) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6(R)-methyl-morpholine;

42) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((6-hydroxy)hexyl)-3-(R)-phenyl-morpholine;

43) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(5-(methylaminocarbonyl)pentyl)-3-(R)-phenyl-morpholine;

44) 4-(3-(1,2,4-triazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;

45) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3,5-dimethyl)benzyloxy)-3-phenyl-morpholine;

46) 4-(3-(1,2,4-triazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;

47) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3,5-di(tert-butyl)benzyloxy)-3-phenyl-morpholine;

48) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

49) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

50) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(trifluoromethyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

51) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(trifluoromethyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

52) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

53) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

54) 4-(2-(imidazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;

55) 4-(4-(imidazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;

56) 4-(2-(imidazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;

57) 4-(4-(imidazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;

58) 4-(2-(imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

59) 4-(4-(imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

60) 4-(2-(imidazolo)methyl)-2-(3-(trifluoro-methyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

61) 4-(4-(imidazolo)methyl)-2-(3-(trifluoro-methyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

62) 4-(2-(imidazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

62) 4-(4-(imidazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

63) 2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenyl-morpholine;

64) 2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine;

65) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylmethyl)-3-(S)-phenylmorpholine;

66) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine;

67) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((2-aminoethyl)aminocarbonylmethyl)-3-(S)-phenyl-morpholine;

68) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((3-aminopropyl)amino carbonylmethyl)-3-(S)-phenyl-morpholine;

69) 4-benzyl-5-(S),6-(R)-dimethyl-3-(S)-phenylmorpholinone and 4-benzyl-5-(R),6-(S)-dimethyl-3-(S)-phenyl-morpholinone;

70) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(S), 6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone;

71) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(R), 6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone;

72) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R), 6-(S)-dimethyl]-3-(S)-phenylmorpholinone;

73) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo) methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone;

74) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone;

75) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone;

76) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(2-(1-(4-benzyl)piperidino)ethyl)-3-(S)-phenylmorpholine;

77) 3-(S)-(4-fluorophenyl)-4-benzyl-2-morpholinone;

78) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzylmorpholine;

79) 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl) morpholine;

80) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine;

81) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((3-pyridyl)methyl carbonyl)-3-(R)-phenylmorpholine;

82) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-(R)-phenylmorpholine;

83) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxypentyl)-3-(R)-phenylmorpholine;

84) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methylaminocarbonylpentyl)-6-oxo-hexyl)-3-(R)-phenylmorpholine;

and pharmaceutically acceptable salts thereof.

TACHYKININ ANTAGONISM ASSAY

The compounds of this invention are useful for antagonizing tachykinins, in particular substance P and neurokinin A in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine and asthma in a mammal in need of such treatment. This activity can be demonstrated by the following assay.

A. Receptor Expression in COS

To express the cloned human neurokinin-1 receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 ul of transfection buffer (135 mM NaCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 2.4 mM K_2HPO_4, 0.6 mM KH_2PO_4, 10 mM glucose, 10 mM HEPES pH 7.4) at 260 V and 950 uF using the IBI GENEZAPPER (IBI, New Haven, CT). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY) in 5% CO_2 at 37°C for three days before the binding assay.

B. Stable Expression in CHO

To establish a stable cell line expressing the cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of 20

ug of the plasmid DNA into CHO cells was achieved by electroporation in 800 ul of transfection buffer suplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 uF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10 % fetal calf serum, 100 U/ml pennicilin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS), 0.7 mg/ml G418 (GIBCO)] in 5% CO_2 at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

C. Assay Protocol using COS or CHO

The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ^{125}I-substance P (^{125}I-SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavallette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200 ul of the cell suspension would give rise to about 10,000 cpm of specific ^{125}I-SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200 ul of cells were added to a tube containing 20 ul of 1.5 to 2.5 nM of ^{125}I-SP and 20 ul of unlabeled substance P

or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1 % polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP_3. CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 0.025 uCi/ml of ^3H-myoinositol by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 0.1 mM with or without the test compound, and incubation is continued at 37°C for 15 min. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 min of incubation at 37°C, the media is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and extracted with $CHCl_3$/methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid and quantitated by beta counter.

The compounds of the present invention are useful in the prevention and treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of tachykinin, in particular substance P, activity.

These conditions may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example AIDS related neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; diseases characterized by neurogenic mucus secretion, such as cystic fibrosis; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues

and disorders related to immune enhancement or suppression, such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorder, motion, surgery, migraine and variations in intercranial pressure; disorders of bladder function such as bladder detrusor hyperreflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine. Hence, these compounds may be readily adapted to therapeutic use for the treatment of physiological disorders associated with an excessive stimulation of tachykinin receptors, especially neurokinin-1, and as neurokinin-1 antagonists the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

For example, the compounds of the present invention may suitably be used in the treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease and Down's

syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, broncho-pneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastro-intestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine.

As calcium channel blocking agents some of the compounds of the present invention are useful in the prevention of treatment of clinical conditions which benefit from inhibition of the transfer of calcium ions across the plasma membrane of cells. These include diseases and disorders of the heart and vascular system such as angina pectoris, myocardial infarction, cardiac arrhythmia, cardiac hypertrophy, cardiac vasospasm, hypertension, cerebrovascular spasm and other ischemic disease. Furthermore, these compounds may be capable of lowering elevated intraocular pressure when administered topically to the hypertensive eye in solution in a suitable ophthalmic vehicle. Also, these compounds may be useful in the reversal of multidrug resistance in tumor cells by enhancing the efficacy of

chemotherapeutic agents. In addition, these compounds may have activity in blocking calcium channels in insect brain membranes and so may be useful as insecticides.

The compounds of the present invention are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example: neuropathy, such as diabetic or peripheral neuropathy and chemotherapy-induced neruopathy; postherpetic and other neuralgias; asthma; osteoarthritis; rheumatoid arthritis; and especially migraine. The compounds of the present invention are also particularly useful in the treatment of diseases characterized by neurogenic mucus secretion, especially cystic fibrosis.

In the treatment of the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for

tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above

containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solution, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically

acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For the treatment of the clinical conditions and diseases noted above, the compounds of this invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

For the treatment of certain conditions it may be desirable to employ a compound of the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of the present invention may be used in conjunction with a bronchodilator, such as a

β_2-adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors. The compound of the present invention and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The compounds of this invention may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize.

In the treatment of a condition associated with an excess of tachykinins, an appropriate dosage level will generally be about 0.001 to 50 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neruotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are as defined above.

ABBREVIATIONS USED IN SCHEMES AND EXAMPLES

Table 1

Reagents:

Et_3N	triethylamine
Ph_3P	triphenylphosphine
TFA	trifluoroacetic acid
NaOEt	sodium ethoxide
DCC	N,N'-dicyclohexylcarbodiimide
DCU	N,N'-dicyclohexylurea
CDI	1,1'-carbonyldiimidazole
MCPBA	m-chloroperbenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Cbz-Cl	benzyl chloroformate
iPr_2NEt or DIEA	N,N-diisopropylethylamine
NHS	N-hydroxysuccinimide
DIBAL	diisobutylaluminum hydride
Me_2SO_4	dimethyl sulfate
HOBt	1-hydroxybenzotriazole hydrate
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

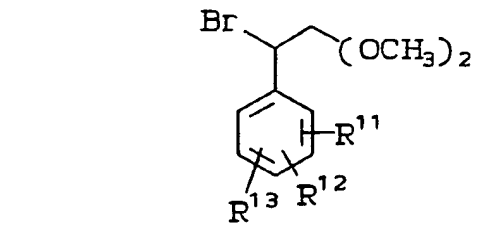
Solvents:

DMF	dimethylformamide
THF	tetrahydrofuran
MeOH	methanol
EtOH	ethanol
AmOH	n-amyl alcohol
AcOH	acetic acid
MeCN	acetonitrile
DMSO	dimethylsulfoxide

Others:

Ph	phenyl
Ar	aryl
Me	methyl
Et	ethyl
iPr	isopropyl
Am	n-amyl
Cbz	carbobenzyloxy (benzyloxy-carbonyl)
BOC	tert-butoxycarbonyl
PTC	phase transfer catalyst
cat.	catalytic
FAB-MS	fast atom bombardment mass spectrometry
rt	room temperature

SCHEME 1



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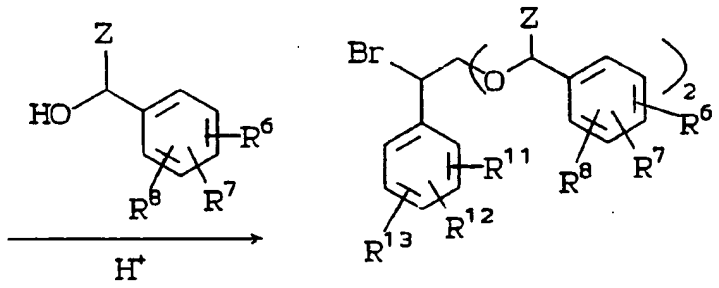
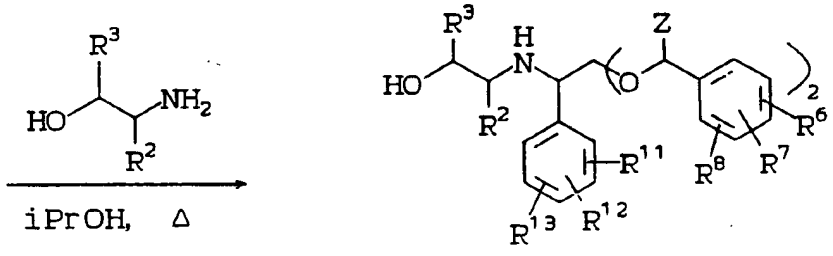


II

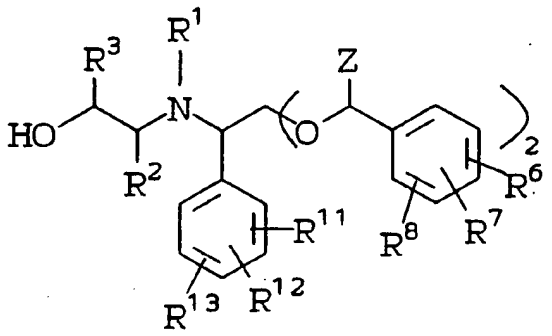


III

R^1-X

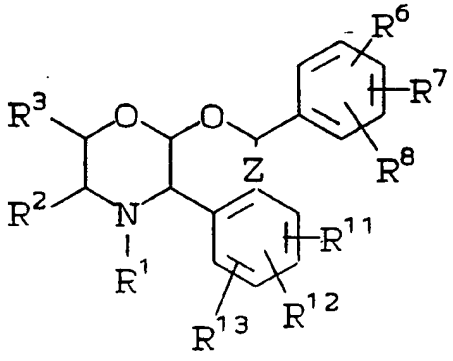
K_2CO_3, iPrOH, Δ

SCHEME 1 (cont'd)



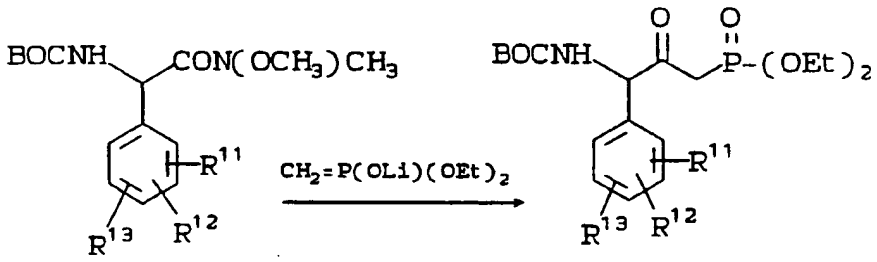
IV

H^+
toluene Δ

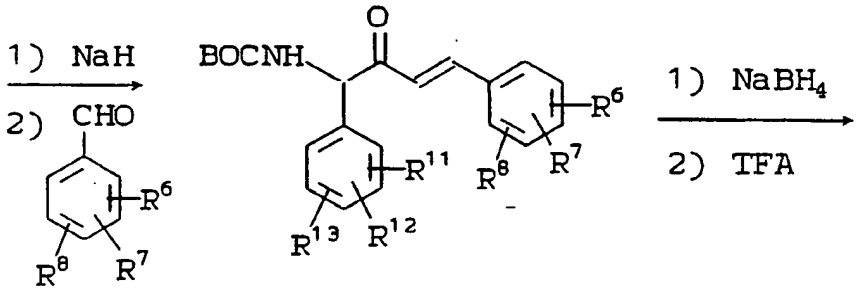


V

SCHEME 2

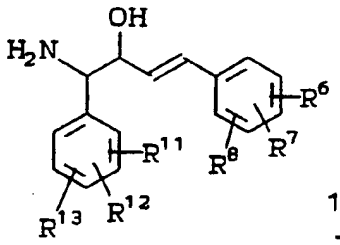


VI VII



VIII

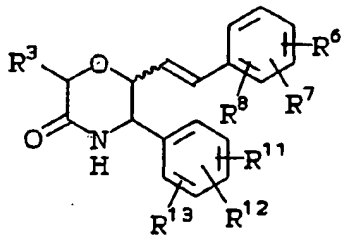
SCHEME 2 (cont'd)



IX

1) NaH, $ClCH(R^3)CO_2Et$

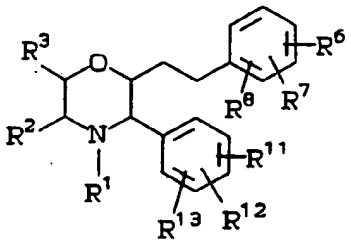
2) Δ



X

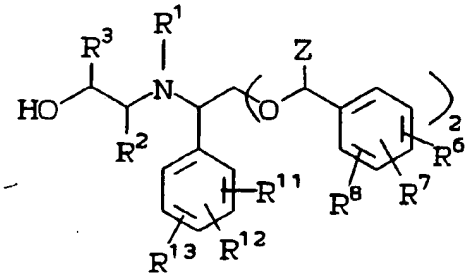
1) H_2, $Pd(OH)_2$

2) BH_3THF



XI

SCHEME 3

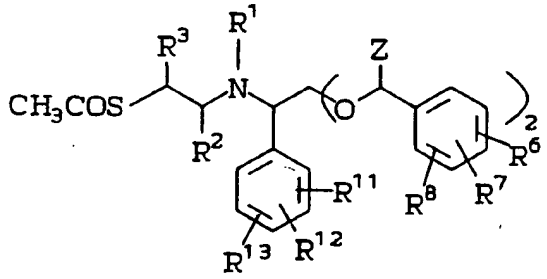


CH_3COSH

Ph_3P, DEAD

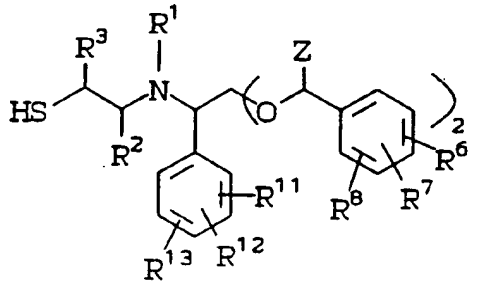
THF

IV



OH^- or [H]

XII

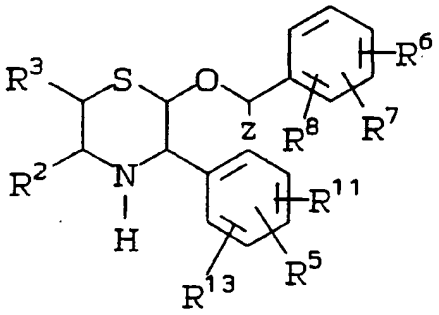


H^+

toluene, Δ

XIII

SCHEME 3 (cont'd)



XIV

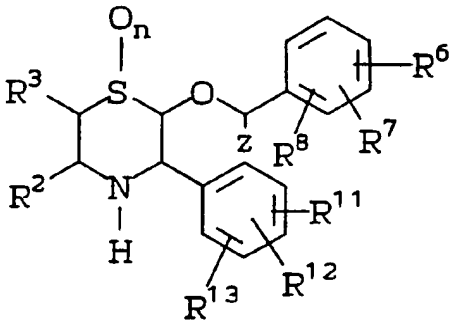
$NaIO_4$

HOAc

rt (n=1)

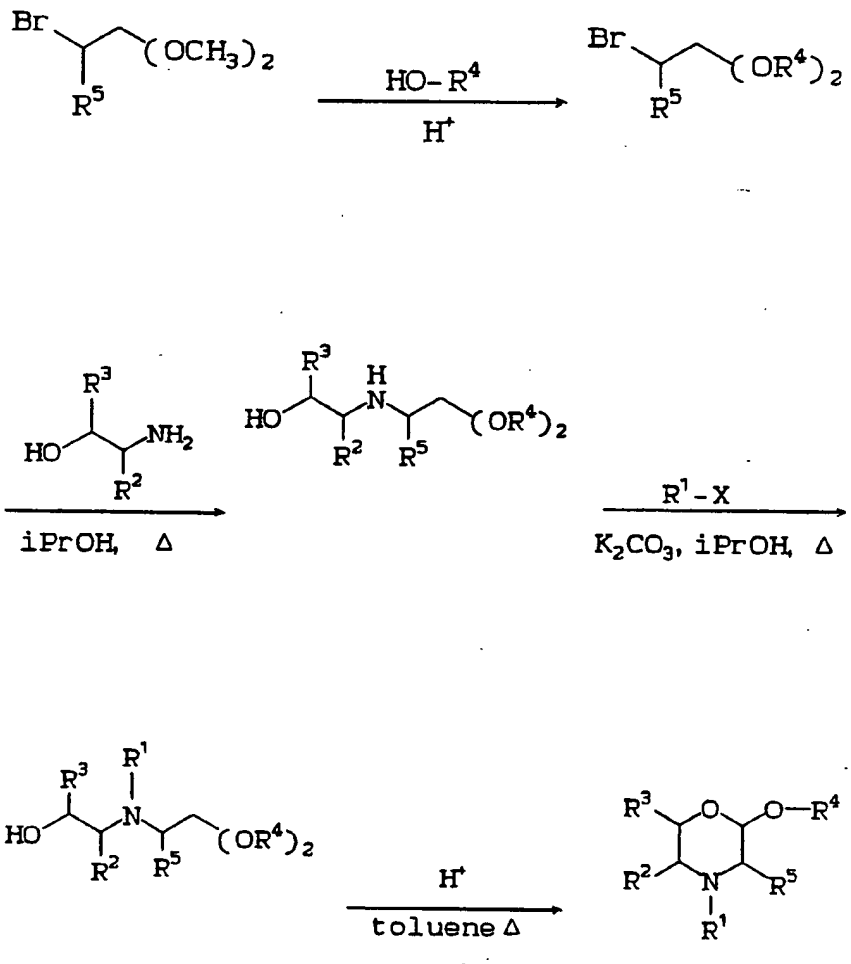
or

60°C (n=2)

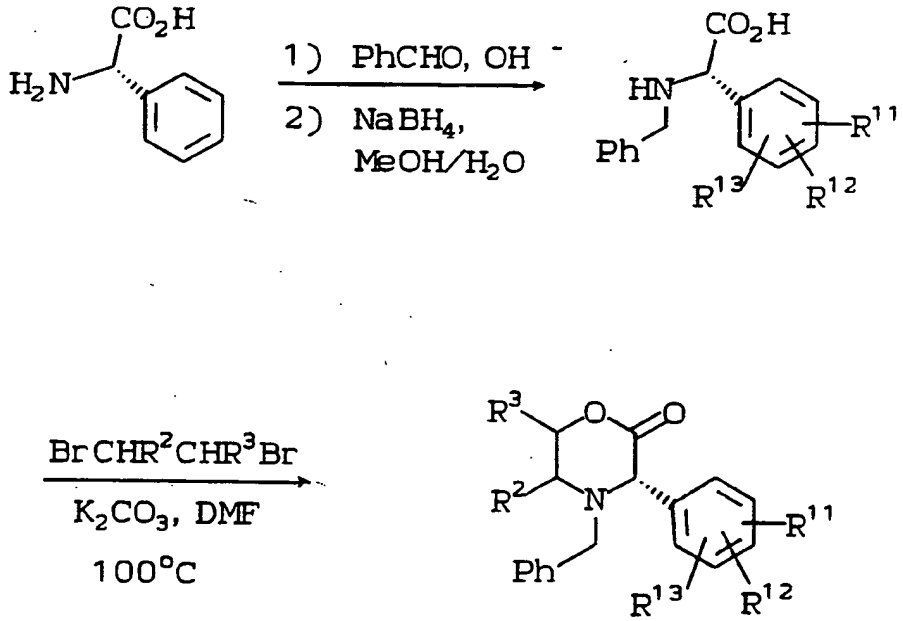


XV

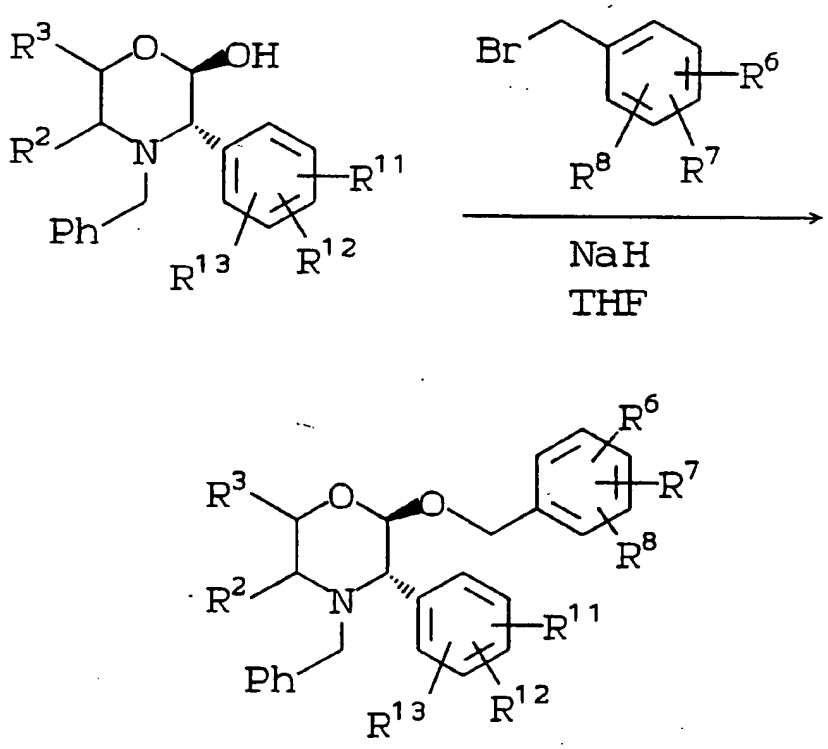
SCHEME 4


Br
(OCH3)2
R5
HO-R4
H+
Br
(OR4)2
R5
R3
HO
NH2
R2
iPrOH, Δ
R3
H
N
HO
(OR4)2
R2
R5
R1-X
K2CO3, iPrOH, Δ
R1
R3
N
HO
(OR4)2
R2
R5
H+
toluene Δ
R3
O
O—R4
R2
N
R5
R1

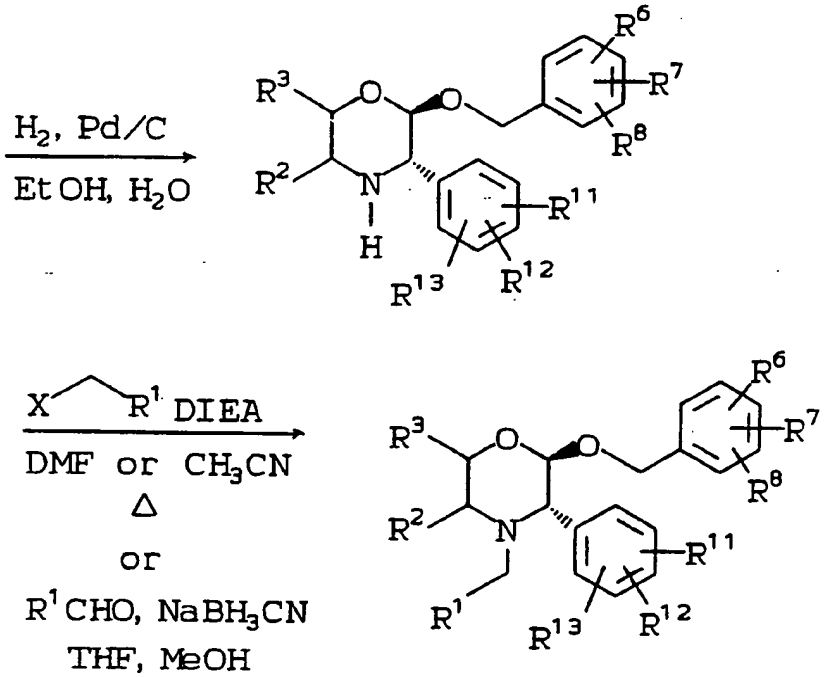
SCHEME 5


CO2H
H2N
1) PhCHO, OH -
2) NaBH4,
MeOH/H2O
CO2H
HN
Ph
R11
R13
R12
BrCHR2CHR3Br
K2CO3, DMF
100°C
R3
O
O
R2
N
Ph
R11
R13
R12
DIBALH
or L-Selectride
-78°C

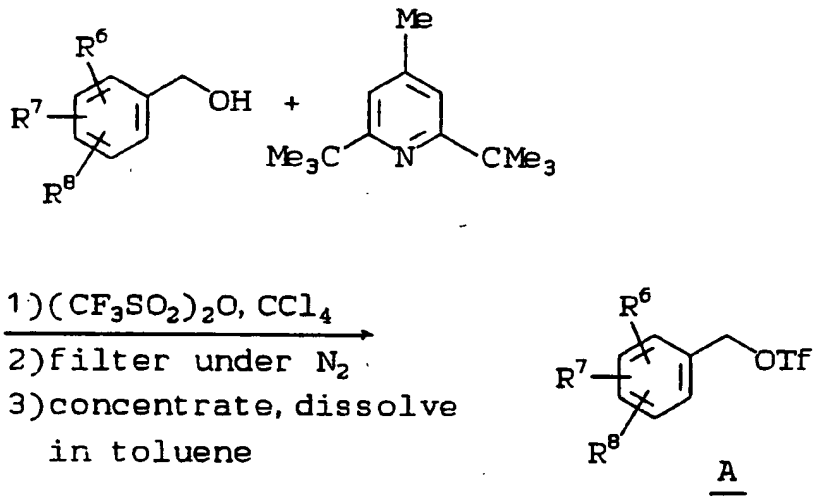
SCHEME 5 (cont'd)



SCHEME 5 (cont'd)

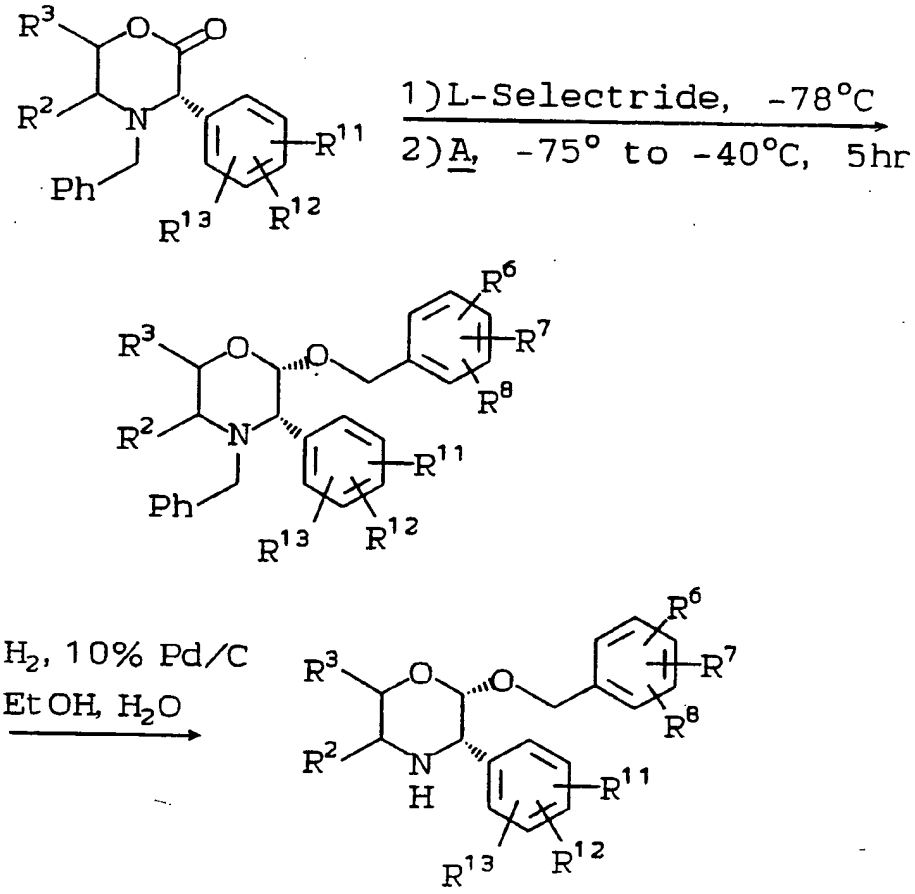


SCHEME 6

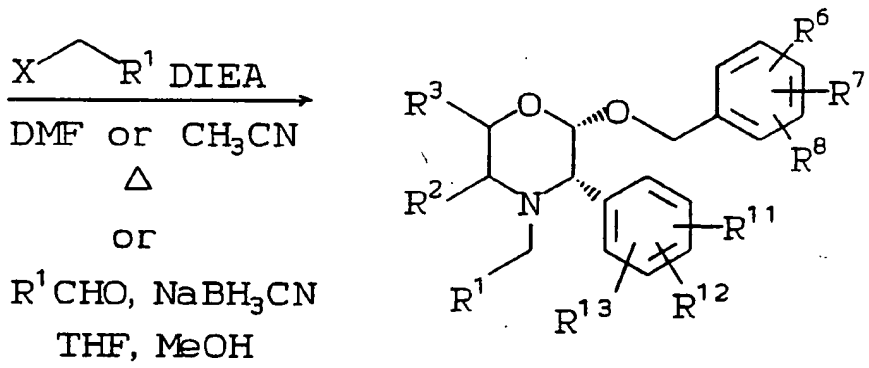

R6
R7
R8
OH
+
Me
Me3C
N
CMe3
1)(CF3SO2)2O, CCl4
2)filter under N2
3)concentrate, dissolve
in toluene
R6
R7
R8
OTf

A

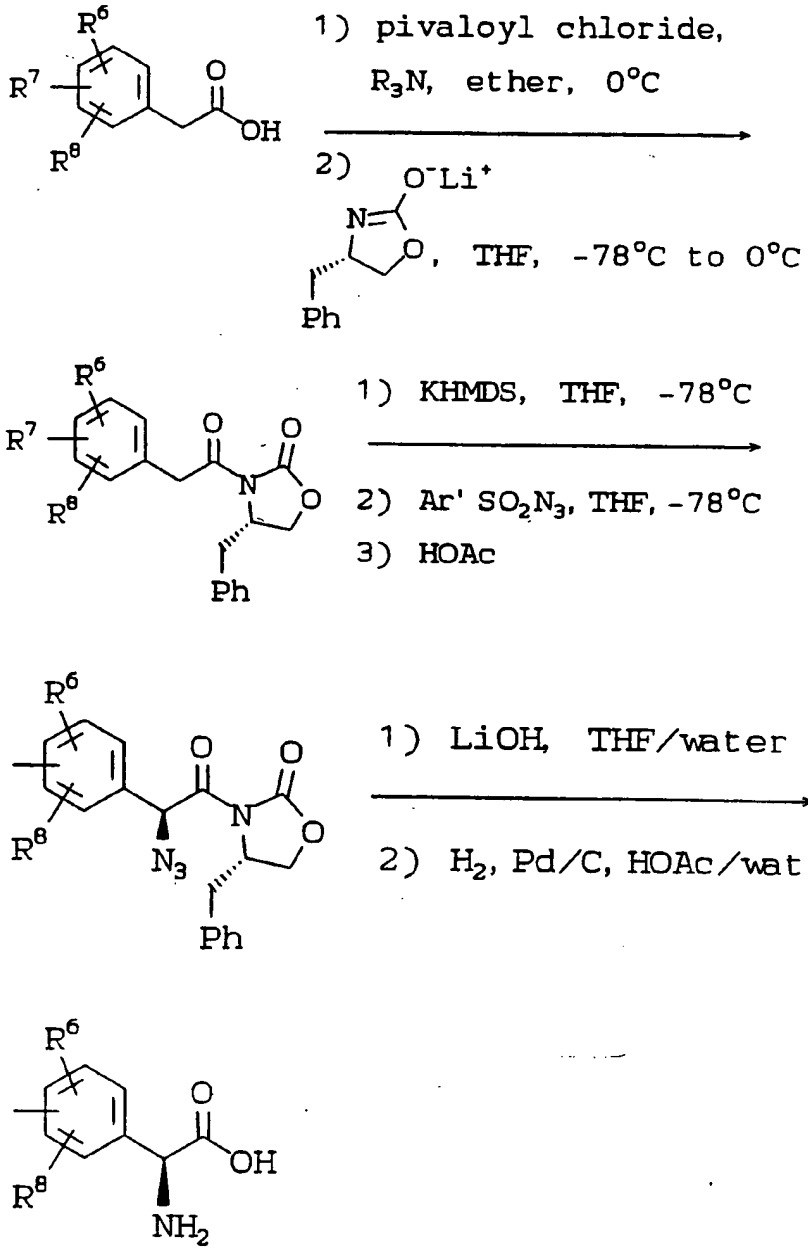
SCHEME 6 (cont'd)



SCHEME 6 (cont'd)



SCHEME 7


R6
R7
R8
O
OH
1) pivaloyl chloride,
R3N, ether, 0°C
2)
O-Li+
N
O
THF, -78°C to 0°C
Ph
1) KHMDS, THF, -78°C
2) Ar' SO2N3, THF, -78°C
3) HOAc
N3
1) LiOH, THF/water
2) H2, Pd/C, HOAc/water
NH2

The compounds of the present invention in which X = Y = O may be prepared by the general route outlined in Scheme 1. Thus, the appropriately substituted a-bromo-phenylacetaldehyde, dimethyl acetal I (prepared using the method of Jacobs in Journal of the American Chemical Society, 1953, 75, 5500) may be converted to the dibenzyl acetal II by stirring I and a slight excess of a benzyl alcohol in the presence of an acid catalyst with concommitant removal of methanol. Alkylation of a substituted amino alcohol by benzyl bromide II may give N-alkyl amino alcohol III; use of a chiral amino alcohol would result in the formation of diastereomers and these can be separated at this (or at a later) stage using standard chromatographic methods. N-Alkylation or N-acylation of III can give the dialkyl- or acyl/alkyl-amino alcohol IV in which the group R^1 may serve as a protecting group or be used as or laborated into a substituent in the final target compound. Cyclization to give substituted morpholine V may be realized by warming a solution of IV and an acid catalyst. Diastereomers of V that may be formed may be separated using standard chromatographic methods. If R^1 is a protecting group, it may be removed using known procedures (Greene, T.W., Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991). If the preparation of I-V results in the formation of enantiomers, these may be resolved by alkylating or acylating V (R^1 = H) with a chiral auxiliary, separating the diastereomers thus formed using known

chromatographic methods, and removing the chiral auxiliary to give the enantiomers of V. Alternatively, the diastereomers of V may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by V and a chiral organic acid.

The compounds of the present invention in which X = O and Y = CH_2 may be prepared by the general route outlined in Scheme 2. Thus, the N-methoxy-N-methyl amide of a protected phenyl glycine VI (prepared from the carboxylic acid via the mixed anhydride according to the procedure of Rapoport in Journal of Organic Chemistry, 1985, 50, 3972) may be used to acylate the lithium enolate of methyl diethylphosphonate to give the ketophosphonate VII. The sodium salt of VII may be condensed with an appropriately substituted benzaldehyde to give the α,ß-unsaturated ketone VIII. Reduction of the ketone and removal of the t-butylcarbamate protecting group may give amino alcohol IX; diastereomers that may form may be separated at this (or at a later) stage using standard chromatographic techniques. Williamson etherification of IX using a substituted chloroacetate, followed by warming, may result in the formation of morpholinone X. Reduction of the double bond and amide carbonyl may be accomplished in a straightforward manner to give the substituted morpholine XI. If the preparation of VI-XI results in the formation of enantiomers, these may be resolved by alkylating or acylating XI (R^1 = H) with a chiral auxiliary, separating the diastereomers thus

formed using known chromatographic methods, and removing the chiral auxiliary to give the enantiomers of XI. Alternatively, the diastereomers of XI may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by XI and a chiral organic acid. If it is desired that R^1 is other than H, the morpholine nitrogen of XI may be further functionalized using standard methods for the alkylation or acylation of secondary amines. If it is desired that R^2 is other than H, morpholinone X may be elaborated into the carbinolcarbamate ($R^1 = RO_2C$, $R^2 = OH$), an intermediate that could be alkylated and would allow for variation in R^2.

The compounds of the present invention in which $X = S-(O)_n$ (n = 0,1,2) and Y = O may be prepared by the general route outlined in Scheme 3. Thus, alcohol IV (prepared in Scheme 1) may be converted to thioacetate XII using known procedures (Volante, R.P. Tetrahedron Letters, 1981, 22, 3119). Cleavage of the ester moiety to afford thiol XIII may be effected with aqueous base or reductively, depending on the restraints imposed by the other functional groups present. Cyclization of XIII to thiomorpholine XIV may be done by warming a solution of XIII and an acid catalyst. Oxidation of XIV using sodium metaperiodate in acetic acid may afford sulfoxide or sulfone XV. Diastereomers of XIV or XV that may be formed may be separated using standard chromatographic methods. If R^1 is a protecting group, it may be removed using known

procedures (Greene, T.W., Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991). If the preparation of XII - XV results in the formation of enantiomers, these may be resolved by alkylating or acylating XIV or XV (R^1 = H) with a chiral auxiliary, separating the diastereomers thus formed using known chromatographic methods, and removing the chiral auxiliary to give the enantiomers of XIV or XV. Alternatively, the diastereomers of XIV or XV may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by XIV or XV and a chiral organic acid.

The compounds of the present invention in which X = Y = O may also be prepared by the general route outlined in Scheme 4. Thus, the appropriately substituted a-bromo-acetaldehyde, dimethyl acetal (prepared using the method of Jacobs in Journal of the American Chemical Society, 1953, 75, 5500) may be converted to the acetal by stirring and a slight excess of the appropriate alcohol in the presence of an acid catalyst with concommitant removal of methanol. Alkylation of a substituted amino alcohol by a bromide may give the N-alkyl amino alcohol; use of a chiral amino alcohol would result in the formation of diastereomers and these can be separated at this (or at a later) stage using standard chromatographic methods. N-Alkylation or N-acylation may give the dialkyl- or acyl/alkyl-amino alcohol in which the group R^1 may serve as a protecting group or be used as or elaborated into a substituent in the

final target compound. Cyclization to give substituted morpholine may be realized by warming a solution with an acid catalyst. Diastereomers that may be formed may be separated using standard chromatographic methods. If R^1 is a protecting group, it may be removed using known procedures (Greene, T.W., Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York, 1991). If the preparation of such compounds results in the formation of enantiomers, these may be resolved by alkylating or acylating the final product (R^1 = H) with a chiral auxiliary, separating the diastereomers thus formed using known chromatographic methods, and removing the chiral auxiliary to give the desired enantiomers. Alternatively, the diastereomers may be separated via fractional crystallization from a suitable solvent of the diastereomeric salts formed by the compound of a chiral organic acid.

One method of synthesizing enantiomerically pure substituted morpholines is illustrated in Scheme 5. Protection of enantiomerically pure phenylglycine as the N-benzyl derivative followed by double alkylation with a 1,2-dibromoethane derivative leads to the morpholinone. Reduction with an active hydride reagent such as diisobutyl aluminum hydride, lithium aluminum hydride, lithium tri(sec-butyl)-borohydride (L-Selectride®) or other reducing agents leads predominantly to the 2,3-trans morpholine derivatives. Alkylation of the alcohol, removal of the protecting group on nitrogen (for example, with a

palladium hydrogenation catalyst or with 1-chloroethyl chloroformate (Olofson in J. Org. Chem., 1984, 2081 and 2795), and alkylation of the nitrogen produces the 2,3-trans compounds.

One method of producing enantiomerically pure 2,3-cis morpholines is illustrated in Scheme 6. In the first step, formation of the trifluoromethanesulfonate ester of the appropiate benzyl alcohol (especially benzyl alcohols which are substituted with electron-withdrawing groups such as $-NO_2$, -F, -Cl, -Br, -COR, $-CF_3$, etc) is carried out in the presence of an unreactive base, in an inert solvent. Other leaving groups such as iodide, mesylate, tosylate, p-nitrophenylsulfonate and the like may also be employed. Appropriate bases include 2,6-di-t-butylpyridine, 2,6-di-t-butyl-4-methylpyridine, diisopropylethylamine, potassium carbonate, sodium carbonate, and the like. Suitable solvents include toluene, hexanes, benzene, carbon tetrachloride, dichloromethane, chloroform, dichloroethane, and the like and mixtures thereof. The filtered solution of the triflate is then added to a solution of the intermediate formed when the morpholinone is contacted with an active hydride reagent such as diisobutyl aluminum hydride, lithium aluminum hydride, or lithium tri(sec-butyl)-borohydride (L-Selectride®) at low temperature, preferably from -78°C to -20°C. After several hours at low temperature, workup and purification provides predominantly 2,3-cis substituted products, which can be carried on to final compounds as shown in Scheme 6.

Enantiomerically pure phenylglycines substituted on the phenyl ring may be prepared by the procedure shown in Scheme 7 (D.A. Evans, et al, J. Am. Chem. Soc., 1990, 112, 4011).

Methods for preparing the nitrogen alkylating agents R^1CH_2X used in Scheme 5 and Scheme 6 are based on known literature methods (for R^1 = 3-(1,2,4-triazolyl) or 5-(1,2,4-triazol-3-one)-yl and X = Cl, see Yanagisawa, I.; Hirata, Y.; Ishii, Y. Journal of Medicinal Chemistry, 1984, 27, 849; for R^1 = 4-((2H)-imidazol-2-one)-yl or 5-(4-ethoxycarbonyl-(2H)-imidazol-2-one)-yl and X = Br, see Ducschinsky, R., Dolan, L.A. Journal of the American Chemical Society, 1948, 70, 657).

The object compounds of Formula I obtained according to the reactions as explained above may be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, tartrate,

tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed in vacuo or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

Although the reaction schemes described herein are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of formula I may render the molecule incompatible with a particular synthetic sequence.

In such a case an alternative route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including reagents, solvent, temperature, and time, should be chosen so that they are consistent with the nature of the functionality present in the molecule.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the instant invention.

EXAMPLE 1

(+/-)-α-Bromo-phenylacetaldehyde, 3,5-bis(trifluoromethyl)benzyl acetal

A solution of 2.50 g (10.2 mmol) of α-bromo-phenylacetaldehyde, dimethyl acetal, 8.00 g (32.8 mmol) of 3,5-bis(trifluoromethyl)benzyl alcohol and 0.50 g (2.6 mmol) of p-toluenesulfonic acid monohydrate in 10 mL of toluene was stirred under vacuum (35 mmHg) at rt for 3 days. The reaction mixture was partitioned between 100 mL of ether and 50 mL of saturated aqueous sodium bicarbonate solution and the layers were separated. The organic layer was washed with 25 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 200 g of silica gel using 9:1 v/v hexane/methylene chloride as the eluant afforded 5.41 g (81%) of the title compound as a solid, mp 79-82°C: ^{1}H NMR 4.47 and 4.62 (AB q, 2 H, J = 12.5), 4.78-4.93 (2 H), 5.09 and 5.21 (AB q, 2 H,

J = 7.7), 7.31-7.44 (m, 7 H), 7.70 (app s, 1 H), 7.82 (app s, 1 H), 7.84 (app s 2 H);
IR (thin film) 1363, 1278, 1174, 1130, 704, 682.
Anal. Calcd for $C_{26}H_{17}BrF_{12}O_2$: C, 46.76; H, 2.23; Br, 11.64; F, 33.70. Found: C, 46.65; H, 2.56; Br, 11.94; F, 34.06.

EXAMPLE 2

(+/-)-N-(2-Hydroxyethyl)-phenylglycinal, 3,5-bis-(trifluoromethyl)benzyl acetal

A solution of 1.50 g (2.2 mmol) of (+/-)-α-bromo-phenylacetaldehyde, 3,5-bis(trifluoromethyl)-benzyl acetal (Example 1), 100 mg (0.67 mmol) of sodium iodide and 3 mL of ethanolamine in 6 mL of isopropanol was heated at reflux for 20 h. The solution was cooled and concentrated to ~25% the original volume in vacuo. The concentrated solution was partitioned between 50 mL of ether and 20 mL of 2 N aqueous sodium hydroxide solution and the layers were separated. The organic layer was washed with 20 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 50 g of silica gel using 65:35 v/v ether/hexane as the eluant afforded 1.18 g (83%) of the title compound as an oil: ^{1}H NMR 2.66 (br s, 2 H), 2.61 and 2.68 (ddAB q, 2 H, J_{AB} = 12.4, $J_{2.61}$ = 6.8, 6.2, $J_{2.68}$ = 6.2, 6.2), 3.57 and 3.66 (ddAB q, 2 H, J_{AB} = 10.8, $J_{3.57}$ = 6.2, 6.2), $J_{3.66}$ = 6.8, 6.2), 4.02 (d, 1 H, J = 7.0), 4.37 and 4.64 (AB q, 2 H, J = 12.5), 4.80 and 4.87 (AB q, 2 H,

J = 12.8), 4.87 (d, 1 H, J = 7.0), 7.31-7.40 (7 H), 7.73 (app s, 1 H), 7.81 (app s, 3 H);
IR (neat) 3342, 1456, 1373, 1278, 1173, 1128, 704, 682;
FAB-MS 650$(M+1)^+$.
Anal. Calcd for $C_{28}H_{23}F_{12}NO_3$: C, 51.78; H, 3.57; N, 2.16; F, 35.11. Found: C, 51.80; H, 3.67; N, 2.10; F, 35.41.

EXAMPLE 3

(+/-)-N-(2-Hydroxyethyl)-N-(prop-2-enyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal

A mixture of 1.45 g (2.2 mmol) of (+/-)-N-(2-hydroxyethyl)-phenylglycinal, 3,5-bis-(trifluoromethyl)benzyl acetal (Example 2), 1.0 g (7.2 mmol) of potassium carbonate, 3.0 mL (35.0 mmol) of allyl bromide and 15 mL of ethanol was stirred at 60 °C for 20 h. The mixture was cooled, partitioned between 100 mL of ether and 25 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 100 mL of ether; the ether extract was dried and combined with the original organic layer. The combined organic layers were concentrated in vacuo. Flash chromatography on 50 g of silica gel using 4:1 v/v hexane/ether as the eluant afforded 1.36 g (88%) of the title compound as an oil: ^1H NMR 2.40 (dt, 1 H, J = 13.2, 2.8), 2.93-3.08 (3 H), 3.30 (ddt, 1 H, J = 12.0, 2.8, 1.6), 3.54 (br m, 2 H), 3.65 (dt, 1 H, J = 10.0, 2.8), 4.23 (d, 1 H, J = 8.4), 4.52 and 4.58

(AB q, 2 H, J = 12.4), 4.85 and 4.95 (AB q , 2 H, J = 12.4), 5.25 (d, 1 H, J = 9.6), 5.28 (d, 1 H, J = 16.4), 5.39 (d, 1 H, J = 8.4), 5.81 (m, 1 H), 7.24-7.40 (7 H), 7.68 (s 1 H), 7.83 (s, 1 H), 7.86 (s, 2 H);

IR (neat) 3457, 1362, 1278, 1174, 1132, 1056, 759, 705, 682; FAB-MS 690$(M+1)^+$.

Anal. Calcd for $C_{31}H_{27}F_{12}NO_3$: C, 53.99; H, 3.95; N, 2.03; F, 33.07. Found: C, 54.11; H, 4.08; N, 1.78; F, 32.75.

EXAMPLE 4

(+/-)-2-(3,5-Bis(trifluoromethyl)benzyloxy)-3-phenyl-morpholine

Step A: A solution of 850 mg (1.2 mmol) of (+/-)-N-(2-hydroxyethyl)-N-(prop-2-enyl)-phenyl-glycinal, 3,5-bis(trifluoromethyl)benzyl acetal (Example 3) and 700 mg (3.7 mmol) of p-toluenesulfonic acid monohydrate in 15 mL of toluene was heated at reflux for 1.5 h. The reaction mixture was cooled and partitioned between 100 mL of ether and 25 mL of saturated aqueous sodium bicarbonate solution. The layers were separated; the organic layer was washed with 25 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 30 g of silica gel using 50:1 v/v hexane/ether as the eluant afforded 426 mg (78%) of the N-allyl morpholines which were used in the next step without further purification.

Step B: A 50 mL 2-necked flask, equipped with a stopper and a short path distillation apparatus, was charged with a solution of the N-allyl morpholines (Example 4, Step A) (540 mg, 1.2 mmol)) and 80 mg (0.09 mmol) tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst) in 25 mL of 4:1 v/v acetonitrile/water. The reaction mixture was heated to boiling and solvent was allowed to distill from the reaction mixture. The volume of the reaction mixture was maintained between 10 and 20 mL by adding solvent through the stoppered inlet. After 1 h and 4 h, the reaction was treated with additional 80 mg portions of the Wilkinson's catalyst. After 6 h, the reaction mixture cooled and partitioned between 75 mL of ether and 50 mL of water. The layers were separated and the organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 75 mL of ether; the extract was dried and combined with the original organic layer. The combined organic layers were concentrated in vacuo. Flash chromatography on 35 g of silica gel using 1:1 v/v ether/hexane as the eluant afforded 200 mg of trans-isomer and 130 mg of a mixture of cis- and trans-isomers (68% total). Chromatography of the mixture on 8 g of silica gel using 4:1 v/v hexane/ether as the eluant afforded 64 mg of cis-V and 57 mg of a mixture of the cis- and trans-isomers of the title compound.

For trans-V: ^{1}H NMR 2.03 (br s, 1 H), 2.94 (ddd, 1 H, J = 11.0, 2.5, 2.5), 3.08 (dt, 1 H, J = 11.0, 3.2), 3.71 (d, 1 H, J = 7.0), 3.83 (dt, 1 H, J = 11.2, 2.8), 4.05 (ddd, 1 H, J = 11.2, 3.2, 3.2), 4.43

(d, 1 H, J = 7.0), 4.53 and 4.88 (AB q, 2 H, J = 13.3), 7.26-7.45 (7 H), 7.70 (s, 1 H);
IR (neat) 3333, 2859, 1456, 1374, 1278, 1173, 1131, 1082, 757, 702, 682;
FAB-MS 406(M+1)$^+$.
Anal. Calcd for $C_{19}H_{17}F_6NO_2$: C, 56.30; H, 4.23; N, 3.46; F, 28.12. Found: C, 56.39; H, 4.28; N, 3.36; F, 28.32.
For cis-V: ^{1}H NMR 2.10 (br s, 1 H), 3.13 (dd, 1 H, J = 12.4, 3.0), 3.26 (dt, 1 H, J = 12.4, 3.6), 3.65 (dd, 1 H, J = 11.6, 3.6), 4.07 (dt, I H, J = 11.6, 3.0), 4.14 (d, 1 H, J = 2.4), 4.52 and 4.82 (AB q, 2 H, J = 13.6), 4.76 (d, 1 H, J = 2.4), 7.30-7.42 (6 H), 7.70 (s, 1 H),
FAB-MS 406(M+1)$^+$.

EXAMPLE 5

(+/-)-2-(3,5-Bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methylcarbox-amido morpholine

A solution of 105 mg (0.26 mmol) of the trans-isomer of (+/-)-2-(3,5-bis(trifluoromethyl)-benzyloxy)-3-phenyl-morpholine (Example 4) and 0.09 mL (0.50 mmol) of N,N-diisopropylethylamine in 3 mL of acetonitrile was treated with 90 mg (0.50 mmol) of iodoacetamide and the resulting solution was stirred at rt for 16 h. The solution was concentrated in vacuo and the residue was partitioned between 20 mL of ethyl acetate and 10 mL of 0.5 N aqueous potassium hydrogen sulfate solution. The layers were separated; the organic layer was washed with 10 mL of 5% aqueous sodium thiosulfate solution, 10 mL of

saturated aqueous sodium bicarbonate solution, 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 5 g of silica gel using 2:1 v/v ethyl acetate/hexane as the eluant afforded 99 mg (82%) of the trans-isomer of the title compound as an oil: ^{1}H NMR 2.56 (dt, 1 H, J = 3.2, 11.6), 2.67 and 3.16 (AB q, 2 H, J = 16.4), 2.96 (dt, 1 H, J = 12.0, 1.6), 3.30 (d, 1 H, J = 7.0), 3.86 (dt, 1 H, J = 3.2, 12.0), 4.08 (ddt, 1 H, J = 11.6, 3.2, 1.6), 4.48 and 4.84 (AB q, 2 H, J = 13.2), 4.49 (d, 1 H, J = 7.0), 5.98 (br s, 1 H), 6.83 (br s, 1 H), 7.33 (app s, 7 H), 7.70 (s, 1 H);
IR (neat) 3445, 2838, 1682, 1278, 1173, 1132, 760, 704, 682; FAB-MS 463 $(M+1)^+$.
Anal. Calcd for $C_{21}H_{20}F_6NO_3$: C, 54.54; H, 4.36; N, 6.06; F, 24.65. Found: C, 54.54; H, 4.52; N, 5.61; F, 24.45.

A similar experiment was carried out on 40 mg (0.99 mmol) of the cis-isomer of (+/-)-2-(3,5-bis-(trifluoromethyl)-benzyloxy)-3-phenyl-morpholine (Example 4) using 0.035 mL (0.2 mmol) of N,N-diisopropylethylamine and 37 mg (0.2 mmol) of iodoacetamide in the reaction. Work-up and flash chromatography afforded 30 mg (65%) of the cis-isomer of the title compound as an oil: ^{1}H NMR 2.54 and 3.04 (AB q , 2 H, J = 16.8), 2.63 (dt, 1 H, J = 3.6, 12.0), 3.04 (d, 1 H, J = 11.6), 3.65 (d, 1 H, J = 2.8), 3.71 (ddt, 1 H, J = 11.6, 3.2, 1.2), 4.21 (dt, 1 H, J = 11.6, 2.4), 4.44 and 4.89 (AB q , 2 H, J = 13.6), 4.71 (d, 1 H, J = 2.8), 5.86 (br s, 1 H), 7.15 (br s, 1 H), 7.27-7.45 (7 H), 7.73 (s, 1 H); FAB-MS 463$(M+1)^+$.

EXAMPLE 6

(+/-)-2-(3,5-Bis(trifluoromethyl)benzyloxy)-3-phenyl-4-(methoxycarbonylmethyl)morpholine

A solution of 150 mg (0.37 mmol) of the trans-isomer of (+/-)-2-(3,5-bis(trifluoromethyl)-benzyloxy)-3-phenyl morpholine (Example 4) (R^1 = H) and 0.18 mL (1.00 mmol) of N,N-diisopropylethylamine in 2 mL of acetonitrile was treated with 0.095 mL (1.00 mmol) of methyl bromoacetate and the resulting solution was stirred at rt for 20 h. The solution was concentrated in vacuo and the residue was partitioned between 20 mL of ethyl acetate and 5 mL of 0.5 N aqueous potassium hydrogen sulfate solution. The layers were separated; the organic layer was washed with 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 10 g of silica gel using 4:1 v/v hexanes/ether as the eluant afforded 164 mg (93%) of the trans-isomer of the title compound as an oil:
^{1}H NMR 2.79 (dt, 1 H, J = 3.2, 11.2), 2.93 (dt, 1 H, J = 11.2, 1.6), 3.52 (d, 1 H, J = 7.2), 3.63 (s, 3 H), 3.92 (dt, 1 H, J = 2.8, 11.6), 4.04 (ddd, 1 H, J = 11.6, 3.2, 1.6), 4.45 and 4.84 (AB q, 2 H, J = 13.2), 4.46 (d, 1 H, J = 7.2), 7.31 - 7.38 (m, 6 H), 7.68 (s, 1 H);
IR (neat) 2861, 1744, 1455, 1375, 1346, 1278, 1170, 887, 759, 704, 682; FAB-MS 478(M+1)$^+$.
Anal. Calcd for $C_{22}H_{21}F_6NO_4$: C, 55.35; H, 4.43; N, 2.93; F, 23.88. Found: C, 55.74; H, 4.50; N, 2.79; F, 24.01.

EXAMPLE 7

N-Methoxy-N-methyl-(N-t-butoxycarbonyl)-phenyl-glycinamide

A solution of 20.0 g (79.7 mmol) of (N-t-butoxycarbonyl)phenylglycine in 150 mL of ethyl acetate at -10 °C was treated with 8.8 mL (79.7 mmol) of 4-methylmorpholine. Isobutylchloroformate (10.3 mL, 79.7 mmol) was added dropwise over 10 minutes maintaining the temperature at -10 °C; the resulting suspension was stirred cold for 15 min. The mixture was treated with 11.6 g (119.0 mmol) of N,O-Dimethyl-hydroxylamine • HCl. A second portion of 4-methyl-morpholine (13.0 mL, 119.0 mmol) was added and the reaction was stirred at -10 °C for 15 min and at 25 °C for 2 h. The reaction mixture was partitioned between 100 mL of ethyl acetate and 100 mL of 10% aqueous citric acid solution and the layers were separated. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate solution, 100 mL of saturated aqueous ammonium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Crystallization from hexanes at -20 °C for 72 h afforded 8.0 g (34%) of the title compound as a solid: ^{1}H NMR 1.40 (s, 9 H), 3.20 (s, 3 H), 3.40 (s, 3 H), 5.80 (m, 2 H), 7.40 (m, 5 H).

EXAMPLE 8

Diethyl (2-oxo-3-t-butoxycarbamido-3-phenyl)-propylphosphonate

A solution of 7.45 mL (51.0 mmol) of diethyl methylphosphonate in tetrahydrofuran at -78 °C was treated with 31.8 mL (51.0 mmol) of 1.6 M n-butyllithium in hexanes solution and the resulting mixture was stirred cold for 30 min. A solution of 4.0 g (14.0 mmol) of N-methoxy-N-methyl-(N-t-butoxy-carbonyl)phenyl-glycinamide (Example 7) in 20 mL of tetrahydrofuran was added and the reaction was stirred at -78°C for 15 min and at 25°C for 15 min. The reaction was quenched with 150 mL of saturated aqueous ammonium chloride solution, diluted with 300 mL of ethyl acetate, and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on silica gel using 7:3 v/v then 4:1 v/v ethyl acetate/hexanes as the eluant afforded 4.8 g (92%) of the title compound as an oil: ^{1}H NMR 1.20-1.42 (15 H), 2.84 (dd, 1 H), 3.20 (dd, 1 H), 4.00-4.20 (m, 4 H), 5.50 (d, 1 H), 5.94 (br s, 1 H), 7.32 (m, 5 H).

EXAMPLE 9

N-t-Butoxycarbonyl-1-phenyl-2-oxo-4-(3,5-bis(tri-fluoromethyl)phenyl)-but-3-enamine

A solution of 4.80 g (12.5 mmol) of diethyl (2-oxo-3-t-butoxycarbamido-3-phenyl)propylphosphonate (Example 8) in 20 mL of THF was added dropwise to a suspension of 1.05 g (26.3 mmol, 60% dispersion in

mineral oil) of sodium hydride in 30 mL of tetrahydrofuran at 0°C. After 15 min, 2.06 mL (12.5 mmol) of 3,5-bis(trifluoromethyl)benzaldehyde was slowly added and the resulting mixture was stirrred cold for 15 min. The reaction was quenched with 50 mL of saturated aqueous ammonium chloride solution, diluted with 50 mL of ethyl acetate, and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on silica gel using 19:1 v/v, then 9:1 v/v ethyl acetate/petroleum ether as the eluant afforded 3.30 g (56%) of the title compound as a solid: ^{1}H NMR 1.40 (s, 9 H), 5.38 (d, 1 H), 5.90 (d, 1 H), 6.80 (d, 1 H), 7.39 (m, 5 H), 7.70 (s, 1 H), 7.84 (s, 3 H).

EXAMPLE 10

1-Phenyl-2-hydroxy-4-(3,5-bis(trifluoromethyl)phenyl)-but-3-enamine • HCl

A solution of 1.00 g (2.1 mmol) of N-t-butoxycarbonyl-1-phenyl-2-oxo-4-(3,5-bis(trifluoromethyl)phenyl)-but-3-enamine (Example 8) in 30 mL of methanol at 0 °C was treated with 241 mg (6.3 mmol) of sodium borohydride. After 30 min, the reaction was quenched with 50 mL of water and concentrated in vacuo to remove the methanol. The mixture was partitioned between 100 mL of ethyl acetate and 50 mL of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Crystallization from ether/hexanes afforded 680 mg

(68%) of the title compound as a 5:1 mixture of diastereomers (each protected as the t-butylcarbamate): ^{1}H NMR (* indicates the resonances of the minor diastereomer) 1.40 (s, 9 H), 4.60 (dd, 1 H), 4.90 (br s, 1 H), 5.20 (br d, 1 H), 6.30 (dd, 1 H), 6.40 (dd. 1 H*), 6.70 (dd, 1 H), 6.80 (dd, 1 H*), 7.40 (m, 5 H), 7.80 (m, 3 H).

A solution of BOC-protected title compound in methanol (saturated with HCl) was allowed to stand for 72 h. The solution was concentrated in vacuo. Recrystallization of the resulting solid from ether/hexane afforded 500 mg (80%) of the title compound • HCl as a solid: ^{1}H NMR 4.20 (br s, 1 H), 4.40 (d, 1 H), 6.20 (dd, 1 H), 6.60 (dd, 1 H), 7.30 (m 5 H), 7.80 (m, 3 H).

The title compound • HCl was dissolved in ethyl acetate and 1 N aqueous sodium hydroxide solution. The layers were separated; the organic layer was dried over magnesium sulfate and concentrated in vacuo to afford the title compound as the free base.

EXAMPLE 11

2-(2-(3,5-Bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine

A solution of 1.95 g (5.2 mmol) of 1-phenyl-2-hydroxy-4-(3,5-bis(trifluoromethyl)phenyl)-but-3-enamine (Example 10) in 20 mL of toluene was added to a suspension of 250 mg (6.2 mmol, 60% dispersion in mineral oil) of sodium hydride in 30 mL of toluene and the resulting mixture was stirred at rt for 15

min. A solution of 0.60 mL (1.15 mol) of ethyl chloroacetate in 5 mL of toluene was slowly added and the resulting mixture was heated at reflux for 3 h. The reaction was cooled, quenched with 50 mL of saturated aqueous ammonium chloride solution, diluted with 50 mL of ethyl acetate and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography using ethyl acetate/hexanes (4:1 v/v, then 3:1 v/v, then 1:1 v/v) then ethyl acetate as the eluant afforded 300 mg of trans-title compound and 800 mg of cis-title compound (55% total), both as solids. For the cis-isomer: 1H NMR 1.20-1.40 (m, 1 H), 1.50-1.62 (m, 1 H), 2.60-2.98 (m, 2 H), 3.86 (dt, 1 H), 4.24 (d, 1 H), 4.34 (dd, 1 H), 4.45 (d, 1 H), 6.40 (br s, 1 H), 7.24 (m, 2 H), 7.40 (m, 3 H), 7.50 (s, 2 H), 7.70 (s, 1 H).

EXAMPLE 12

3-Phenyl-2-(2-(3,5-bis(trifluoromethyl)phenyl)ethyl)-morpholine

A solution of 95 mg (0.23 mmol) of 2-(2-(3,5-bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine (Example 11) in 10 mL of 1:1 v/v ethanol/ethyl acetate was treated with 10 mg of palladium hydroxide and the resulting mixture was stirred under an atmosphere of hydrogen for 2 h. The catalyst was filtered and the filtrate was concentrated in vacuo. The crude product was used directly without further purification.

A solution of 65 mg of the crude morpholinone was dissolved in 10 mL of tetrahydrofuran was treated with 0.84 mL of 1 M borane•tetrahydrofuran complex solution in tetrahydrofuran and the resulting solution was heated at reflux for 16 h. The reaction was quenched by adding 10 mL of methanol and 70 mg of potassium carbonate and heating the resulting mixture at reflux for 3 h. All volatiles were removed in vacuo and the residue was partitioned between 20 mL of ethyl acetate and 10 mL of saturated ammonium chloride solution. The organic layer was separated, dried over sodium carbonate, and concentrated in vacuo. The residue was dissolved in saturated HCl in methanol and concentrated in vacuo. The residue was triturated with ether; the resulting solid was filtered and dried to afford 32 mg (46%) of the title compound • HCl, mp 114-116°C: ^{1}H NMR 1.42 (m, 1 H), 1.66-1.84 (m, 1 H), 2.70-2.94 (m, 2 H), 3.00 (m, 1 H), 3.30-3.46 (m, 1 H), 3.80-3.94 (m, 2 H), 4.10 (m, 1 H), 4.20 (d, 1 H), 7.40 (m, 3 H), 7.64 (m, 5 H); CI-MS 402$(M+1)^+$.

EXAMPLE 13

N-Benzyl-(S)-phenylglycine

A solution of 1.51 g (10.0 mmol) of (S)-phenylglycine in 5 mL of 2 N aqueous sodium hydroxide solution was treated with 1.0 mL (10.0 mmol) of benzaldehyde and stirred at room temperature for 20 minutes. The solution was diluted with 5 mL of methanol, cooled to 0°C, and carefully treated with 200 mg (5.3 mmol) of sodium borohydride. The

cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with 20 mL of water and extracted with 2x25 mL of methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid to pH 6 and the solid that precipitated was filtered, washed with 50 mL of water, 50 mL of 1:1 v/v methanol/ethyl ether and 50 mL of ether, and dried to afford 1.83 g (76%) of product, mp 230-232°C.

Analysis:

Calcd for $C_{15}H_{15}NO_2$:	C-74.66	H-6.27	N-5.81
Found:	C-74.17	H-6.19	N-5.86

EXAMPLE 14

3-(S)-Phenyl-4-benzyl-2-morpholinone

A mixture of 4.00 g (16.6 mmol) of N-benzyl-(S)-phenylglycine (from Example 13), 5.00 g (36.0 mmol) of potassium carbonate, 10.0 mL of 1,2-dibromoethane and 25 mL of N,N-dimethylformamide was stirred at 100 °C for 20 hours. The mixture was cooled and partitioned between 200 mL of ethyl ether and 100 mL of water. The layers were separated and the organic layer was washed with 3x50 mL of water, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on 125 g of silica gel eluting with 9:1 v/v, then 4:1 v/v hexanes/ethyl ether to afford 2.41 g (54%) of the product as a solid, mp 98-100°C.

Mass Spectrum (FAB): m/Z 268 (M+H, 100%).

^1H NMR ($CDCl_3$, 200 MHz, ppm): d 2.54-2.68 (m, 1H),

2.96 (dt, J= 12.8, 2.8, 1H), 3.14 (d, J= 13.3, 1H), 3.75 (d, J= 13.3, 1H), 4.23 (s, 1H), 4.29-4.37 (m, 1H), 4.53 (dt, J= 3.2, 11.0), 7.20-7.56 (m, 10H).

Analysis:

Calcd for $C_{17}H_{17}NO_2$:	C-76.38	H-6.41	N-5.24
Found:	C-76.06	H-6.40	N-5.78

EXAMPLE 15

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

Step A 3,5-Bis(trifluoromethyl)benzyl alcohol, trifluoromethanesulfonate ester

A solution of 1.00g (4.1 mmole) of 3,5-bis(trifluoromethyl)benzyl alcohol and 1.05g (5.12 mmole) of 2,6-di-t-butyl-4-methylpyridine in 45 mL of dry carbon tetrachloride under a nitrogen atmosphere was treated with 0.74 mL (4.38 mmole) of trifluoromethanesulfonic anhydride at room temperature. A white precipitate formed shortly after the addition of the anhydride. After 90 min, the slurry was filtered under nitrogen with a Schlenk filter, and the filtrate was concentrated in vacuo. The residue, which was a two-phase oil, was dissolved under nitrogen in 10 mL of dry toluene. The resulting clear solution was used immediately in Step B below.

Step B 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A solution of 0.500 g (1.87 mmole) of N-benzyl-3-(S)-phenylmorpholin-2-one (from Example 14) in 10 mL of dry THF was cooled to -75°C under nitrogen and was treated dropwise with 2.06 mL (2.06 mmole) of a 1M solution of lithium tri(sec-butyl)-borohydride (L-Selectride®) in THF. After stirring the solution at -75°C for 30 min, a solution of 3,5-bis(trifluoromethyl)benzyl alcohol, trifluoromethanesulfonate ester in toluene was added by cannula so that the internal temperature was maintained below -60°C. The resulting solution was stirred at -75°C for 1 hr and then between -38°C and -50°C for 2 hr. The solution was then poured into a mixture of 25 mL of ethyl acetate and 20 mL of saturated aqueous sodium bicarbonate, and the layers were separated. The aqueous phase was extracted with 2x30 mL of ethyl acetate, the combined organic layers were dried over sodium sulfate, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on 130 g of silica eluting with 2 L of 100:5 hexanes:ethyl acetate to give 0.68 g (73%) of an oil, which by ^1H NMR is a 20:1 mixture of cis:trans morpholines.
^1H NMR ($CDCl_3$, 400 MHz, ppm): δ major (cis) isomer: 2.37 (td, J= 12, 3.6, 1H), 2.86 (app t, J= 13, 2H), 3.57 (d, J= 2.6, 1H), 3.63 (dq, J= 11.3, 1,6, 1H), 3.89 (d, J= 13.3, 1H), 4.12 (td, J= 11.6, 2.4, 1H), 4.40 (d, J= 13.6, 1H), 4.69 (d, J= 2.9, 1H), 4.77 (d, J= 13.6), 7.2-7.4 (m, 8H), 7.43 (s, 2H), 7.55 (br d, 2H), 7.69 (s, 1H).

Step C 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A mixture of 0.68 g (1.37 mmole) of 4-benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl morpholine and 280 mg of 10% Pd/C in 36 mL of 97:3 ethanol:water was stirred under one atmosphere of hydrogen for 15 hr. The mixture was filtered through Celite, the filter cake was washed generously with ethanol, and the filtrated was concentrated in vacuo. The residue was purified by flash chromatography on 68 g of silica eluting with 1L of 33:67 hexanes: diethyl ether, then 1L of 25:75 hexanes: diethyl ether to give 0.443 g (80%) of an oil, which by ^1H NMR was pure cis morpholine. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.8 (br s, 1H), 3.10 (dd, J= 12.5, 2.9, 1H), 3.24 (td, J= 12.2, 3.6, 1H), 3.62 (dd, J= 11.3, 2.5, 1H), 4.04 (td, J= 11.7, 3, 1H), 4.11 (d, J= 2.4, 1H), 4.49 (d, J= 13.5, 1H), 4.74 (d, J= 2.5, 1H), 4.80 (d, J= 13.3, 1H), 7.25-7.40 (m, 5H), 7.40 (s, 2H), 7.68 (s, 1H).

Analysis:

Calcd for $C_{19}H_{17}F_6NO_2$: C-56.30 H-4.23 N-3.46 F-28.12

Found: C-56.20 H-4.29 N-3.34 F-27.94

EXAMPLE 16

2(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3(R)-phenyl-morpholine

The title compound was prepared from (R)-phenylglycine employing the procedures of Examples 13, 14 and 15.

EXAMPLE 17

4-(3-(1,2,4-Triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

Step A N-Formyl-2-chloroacetamidrazone

A solution of 5g (66.2 mmole) of chloroacetonitrile in 30 mL of dry methanol was cooled to 0°C under nitrogen and was treated with 0.1g (1.8 mmole) of sodium methoxide. The mixture was allowed to warm to room temperature and was stirred for 30 min, and 0.106 mL (1.8 mmole) of acetic acid was added. To the resulting mixture was then added 3.9g (64.9 mmole) of formic hydrazide, and the material was stirred for 30 min. The reaction mixture was concentrated in vacuo to a solid, and was used as such in Step B below.

Step B 4-(3-(1,2,4-Triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A solution of 0.295g (0.73 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl morpholine (from Example 15) in 10 mL of dry DMF was treated with 0.302g (2.18 mmole) of anhydrous potassium carbonate and then 0.168g (1.24 mmole) of N-formyl-2-chloroacetamidrazone (from Example 17, Step A) and the suspension was stirred at 60°C for 4 hr. The mixture was then heated to 120°C for 4.5 hr. After cooling, the reaction was diluted with 80 mL of ethyl acetate and the organic layer was washed with 3x20 mL of water. The organic layer was dried

over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on 67 g of silica eluting with 1.5 L of 100:2 methylene chloride:methanol to give 0.22g of a yellow solid, which was recrystallized from hexanes/methylene chloride to give 0.213g (60%) of a white crystalline solid, mp 134-135°C.
Mass Spectrum (FAB): m/Z 487 (M+H, 100%), 259 (35%), 243 (65%), 227 (40%), 174 (25%).
^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.67 (td, J= 11.9, 3.4, 1H), 2.90 (br d, J= 11.7, 1H), 3.43 (d, J= 15.2, 1H), 3.66 (app dd, J= 13, 1.9, 2H), 3.88 (d, J= 15.1, 1H), 4.17 (td, J= 11.7, 2.3, 1H), 4.42 (d, J= 13.5, 1H), 4.69 (d, J= 2.6, 1H), 4.77 (d, J= 13.5, 1H), 7.30-7.50 (m, 7H), 7.70 (s, 1H), 7.94 (s, 1H).

EXAMPLE 18

4-(3-(5-Oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenylmorpholine

Step A N-Methylcarboxy-2-chloroacetamidrazone

A solution of 5.0 g (66.2 mmol) of chloroacetonitrile in 35 mL of dry methanol was cooled to 0°C and was treated with 0.105g (1.9 mmol) of sodium methoxide. The ice-bath was removed and the mixture was alowed to stir at room temperature for 30 minutes. To the reaction was then added 0.110 mL (1.9 mmol) of acetic acid and then 5.8 g (64.9 mmol) of methyl hydrazinecarboxylate. After stirring 30 minutes at room temperature, the suspension was concentrated in vacuo, and placed on the high-vac

line overnight, to give 10.5 g (98%) of a yellow powder, which was employed in Step C below.
^{1}H NMR (CD_3OD, 400 MHz, ppm): δ 3.71 (s, 3H), 4.06 (s, 2H).

Step B 4-(2-(N-Methylcarboxy-acetamidrazono)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A solution of 2.30 g (5.7 mmol) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (from Example 15), 1.13 g (6.8 mmol) of N-methylcarboxy-2-chloroacteamidrazone (from Step A), and 1.50 mL (8.6 mmol) N,N-diisopropylethylamine in 25 mL of acetonitrile was stirred at room temperature for 20 hours. The product, which had preciptated, was filtered, washed with 5 mL of ice cold acetonitrile and dried to give 1.83 g of a white solid. The filtrate was concentrated in vacuo and the residue was partitioned between 50 mL of methylene chloride and 20 mL of water. The layers were separated and the organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 50 mL of methylene chloride; the extract was dried, combined with the original organic layer, and the combined organics were concentrated in vacuo. The residue was purified by flash chromatography on 30 g of silica gel eluting with 50:1:0.1 v/v/v methylene chloride/methanol/ammonium hydroxide to afford an additional 1.09 g of product (96% total).
Mass Spectrum (FAB): m/Z 535 (M+H, 100%), 462 (16%), 291 (30%), 226 (35%), 173 (25%).
^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.53 (dt, J= 3.5,

12.2, 1H), 2.59 (d, J= 14.6, 1H), 2.94 (d, J= 11.8, 1H), 3.37 (d, J= 14.6, 1H), 3.58 (d, J= 2.8), 1H), 3.62-3.72 (m, 1H), 3.75 (s, 3H), 4.16 (dt, J= 2.2, 11.8, 1H), 4.44 (d, J= 13.2, 1H), 4.70 (d, J= 2.8, 1H), 4.79 (d, J= 13.2), 5.55 (br s, 2H), 7.30-7.46 (m, 7H), 7.72 (s, 1H).

Step C 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

A solution of 2.89 g (5.4 mmol) of 4-(2-(N-methylcarboxy-acetamidrazono)-2-(S)-(3,5-bis(trifluoromethyl) benzyloxy)-3-(S)-phenylmorpholine (from Step B) in 36 mL of xylenes was heated at reflux for 1.5 hours. The solution was cooled and concentrated in vacuo. The residue was taken up in 50 mL of 3:1 v/v hexanes/ethyl acetate which caused crystallization of the product. The product was filtered and dried to afford 1.85 g of a solid. Recrystallization of the solid from 30 mL of 4:1 v/v hexanes/ethyl acetate afforded 1.19 g of pure product as a white solid, mp= 156-157°C. All of the crystallization liquors were combined and concentrated in vacuo. The residue was purified by flash chromatography on 30 g of silica gel eluting with 50:1:0.1 v/v/v methylene chloride/-methanol/ammonium hydroxide to afford an additional 0.69 g of a solid. Three recrystallizations from 20 mL of 4:1 v/v hexanes/ethyl acetate afforded an additional 0.39 g of pure product as a white solid (58% total).

Mass Spectrum (FAB): m/Z 503 (M+H), 259 (55%), 226 (40%), 160 (30%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.57 (app t, J= 9.6, 1H), 2.87-2.97 (m, 2H), 3.58-3.71 (m, 3H), 4.18 (app t, J= 10.4, 1H), 4.46 (d, J= 13.6), 4.68 (d, J= 2.8, 1H), 4.85 (d, J= 13.6, 1H), 7.30-7.45 (m, 7H), 7.64 (s, 1H), 10.40 (br s, 1H), 10.73 (br s, 1H).

EXAMPLE 19

N-(2-(R)-Hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal

A mixture of 1.00 g (1.5 mmol) of (+/-)-a-bromo-phenylacetaldehyde, 3,5-bis(trifluoromethyl)-benzyl acetal (from Example 12), 1.25 mL of (R)-1-amino-2-propanol, 225 mg (1.5 mmol) of sodium iodide, and 3.75 mL of isopropanol was heated at reflux for 20 h. The solution was cooled and concentrated to ~25% the original volume in vacuo. The concentrated solution was partitioned between 50 mL of ether and 20 mL of 2 N aqueous sodium hydroxide solution and the layers were separated. The organic layer was washed with 20 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 50 g of silica gel using 65:35 v/v ether/hexane as the eluant afforded 948 mg (95%) of the product as a 1:1 mixture of inseparable diastereomers.

Mass Spectrum (FAB): m/Z 664 (M+H, 25%), 420 (20%), 226 (100%).

EXAMPLE 20

N-(2-(S)-Hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal

Substitution of (S)-1-amino-2-propanol for (R)-1-amino-2-propanol in an experiment identical to the preceding example afforded 940 mg (95%) of the product as a 1:1 mixture of diastereomers.

EXAMPLE 21

N-(2-(R)-Hydroxypropyl)-N-(prop-2-enyl)-(R)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal and N-(2-(R)-Hydroxypropyl)-N-(prop-2-enyl)-(S)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal

A mixture of 933 mg (1.40 mmol) of N-(2-(R)-hydroxy-propyl)-phenylglycinal, 3,5-bis(trifluoromethyl)-benzyl acetal (from Example 19), 1 mL of allyl bromide, 600 mg (4.3 mmol) of potassium carbonate, and 5 mL of ethanol was stirred at 60°C for 20 hours. The mixture was cooled, partitioned between 100 mL of ethyl ether and 25 mL of water and the layers were separated. Flash chromatography on 50 g of silica gel using 20:1 v/v ether/hexanes as the eluant afforded 380 mg of the (R,R)-amino alcohol (R_f = 0.72 with 3:2 v/v ether/hexanes as the eluant), 220 mg of the (R,S)-amino alcohol (R_f = 0.62 with 3:2 v/v ether/hexanes as the eluant), and 285 mg of a mixture of the disastereomeric amino alcohols.

For the (R,R)-amino alcohol:
Mass Spectrum (FAB): m/Z 704(M+H).
IR (neat) 3476, 2932, 1624, 1454, 1361, 1278, 1175, 1132, 760, 704, 682.
^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.12 (d, 3 H, J = 6.4), 2.19 and 2.62 (dAB q, 2 H, J_{AB} = 13.0, $J_{2.19}$ = 2.3, $J_{2.62}$ = 10.4), 2.97 (dd, 1 H, J = 14.0, 8.8), 3.25 - 3.30 (m, 1 H), 3.76 (s, 1 H), 3.77 - 3.85 (m, 1 H), 4.21 (d, 1 H, J = 8.8), 4.49 and 4.55 (AB q, 2 H, J = 12.4), 4.86 and 4.92 (AB q, 2 H, J = 12.4), 5.27 - 5.33 (m, 2 H), 5.39 (d, 1 H, J = 8.8), 5.79 - 5.89 (m, 1 H), 7.21 - 7.26 (m, 4 H), 7.35 - 7.40 (m, 3 H), 7.67 (s, 1 H), 7.81 (s, 1 H), 7.85 (s, 2 H).
Analysis: Calcd for $C_{32}H_{29}F_{12}NO_3$: C, 54.63; H, 4.15; N, 1.99; F, 32.41. Found: C, 54.72; H, 3.94; N, 1.95; F, 32.17.

For the (R,S)-amino alcohol:
Mass Spectrum (FAB): m/Z 704(M+1).
IR (neat) 3451, 2931, 1624, 1454, 1362, 1277, 704, 683.
^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.09 (d, 3 H, J = 6.0), 2.48 and 2.71 (dAB q, 2 H, J_{AB} = 13.2, $J_{2.48}$ = 9.6, $J_{2.62}$ = 3.6), 3.05 (dd, 1 H, J = 14.4, 6.8), 3.34 - 3.39 (m, 1 H), 3.35 (s, 1 H), 3.76 - 3.81 (m, 1 H), 4.21 (d, 1 H, J = 8.4), 4.50 and 4.54 (AB q, 2 H, J = 12.8), 4.86 and 4.96 (AB q, 2 H, J = 12.4), 5.10 - 5.17 (m, 2 H), 5.39 (d, 1 H, J = 8.4), 5.68 - 5.78 (m, 1 H), 7.23 - 7.32 (m, 4 H), 7.34 - 7.39 (m, 3 H), 7.69 (s, 1 H), 7.83 (s, 1 H), 7.86 (s, 2 H).
Analysis: Calcd for $C_{32}H_{29}F_{12}NO_3$: C, 54.63; H, 4.15; N, 1.99; F, 32.41. Found: C, 54.80; H, 4.16; N, 1.90; F, 32.36.

EXAMPLE 22

N-(2-(S)-Hydroxypropyl)-N-(prop-2-enyl)-(S)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal and N-(2-(S)-Hydroxypropyl)-N-(prop-2-enyl)-(R)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal

Substitution of 880 mg (1.33 mmol) of N-(2-(S)-hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal (Example 20) for the N-(2-(R)-hydroxypropyl)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal in the procedures of the preceding example afforded 281 mg of the (S,S)-amino alcohol (R_f = 0.72 with 3:2 v/v ether/hexanes as the eluant), 367 mg of the (S,R)-amino alcohol (R_f = 0.62 with 3:2 v/v ether/hexanes as the eluant), and 197 mg of a mixture of the disastereomeric amino alcohols.

EXAMPLE 23

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine and 2-(S)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine

Step A 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine and 2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine

A solution of 355 mg (0.50 mmol) of N-(2-(R)-hydroxypropyl)-N-(2-propenyl)-(R)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal (from Example 21) and 285 mg (1.5 mmol) of p-toluensulfonic acid monohydrate in 5 mL of toluene was heated at reflux for 40 min. The solution was cooled and partitioned between 40 mL of ether and 15 mL of saturated aqueous sodium bicarbonate solution. The layers were separated; the organic layer was washed with 10 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 10 g of silica gel using 19:1 v/v hexanes/ether as the eluant afforded 122 mg of (2R,3R,6R) product (R_f = 0.53 with 4:1 v/v hexanes/ether as the eluant) and 62 mg of the (2S,3R,6R) product (R_f = 0.23 with 4:1 v/v hexanes/ether as the eluant).

For the <u>(2R,3R,6R) product</u>:
Mass Spectrum (FAB): m/Z 460 (M+H, 65%)
^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.35 (d. 3 H, J = 6.4), 2.53 and 2.63 (dAB q, 2 H, J_{AB} = 12.0, $J_{2.53}$ = 3.2, $J_{2.63}$ = 6.8), 2.83 - 2.96 (m, 2 H), 3.60 (d, 1 H, J = 4.0), 4.27 - 4.32 (m, 1 H), 4.57 and 4.84 (AB q, 2 H, J = 13.2), 4.87 (d, 1 H, J = 4.0), 5.08 - 5.13 (m, 2 H), 5.76 - 5.86 (m, 1 H), 7.31 - 7.37 (m, 3 H), 7.50 - 7.52 (m, 2 H), 7.58 (s, 2 H), 7.71 (s, 1 H).

For the <u>(2S,3R,6R) product</u>:
Mass Spectrum (FAB): m/Z 460 (M+H, 65%)
^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.37 (d. 3 H, J = 6.8),

2.48 - 2.50 (m, 2 H), 2.74 and 3.01 (dtAB q, 2 H, J = 6.4, 1.2, 12.4) 3.84 (d, 1 H, J = 3.6), 3.92 - 3.99 (m, 1 H), 4.70 and 4.93 (AB q, 2 H, J = 13.6), 4.97 (d, 1 H, J = 3.6), 5.08 - 5.14 (m, 2 H), 5.74 - 5.84 (m, 1 H), 7.28 - 7.36 (m, 3 H), 7.43 - 7.46 (m, 2 H), 7.64 (s, 2 H), 7.75 (s, 1 H).

Step B 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine

A solution of 115 mg (0.25 mmol) of the 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine (from Example 23, Step A) and 230 mg (0.25 mmol) of tris(triphenylphosphine)rhodium chloride in 15 mL of 4:1 v/v acetonitrile/water was heated at reflux for 30 min. The reaction was cooled and partitioned between 50 mL of ethyl acetate and 15 mL of water. The layers were separated and the organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 2 x 25 mL of ethyl acetate; the extracts were dried and combined with the original organic layer. The combined organics were concentrated in vacuo. The residue was filtered through a pad of silica gel (~ 20 g) using 2:1 v/v ether/hexanes as the solvent. The filtrate was concentrated; flash chromatography on 5 g of silica gel using 17:3 v/v hexanes/ether as the eluant afforded 67 mg (64%) of 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine as an oil.

Mass Spectrum (FAB): m/Z 420 (M+H, 90%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.21 (d, 3 H, J = 6.4),

2.02 (br s, 1 H), 2.67 and 2.77 (dAB q, 2 H, J_{AB} = 13.2, $J_{2.67}$ = 8.8, $J_{2.77}$ = 3.2), 3.89 (d, 1 H, J = 2.4), 4.07 - 4.15 (m, 1 H), 4.68 and 4.90 (AB q, 2 H, J = 12.8), 5.03 (d, 1 H, J = 2.4), 7.28 - 7.38 (m, 3 H), 7.51 - 7.53 (m, 2 H), 7.77 (s, 2 H), 7.79 (s, 1 H).

Step C 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine

A similar reaction was carried out using 55 mg (0.12 mmol) of 2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(R)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine (from Example 23, Step A) and 111 mg (0.12 mmol) of tris(triphenylphosphine)rhodium chloride in 12 mL of 4:1 v/v acetonitrile/water. Flash chromatography on 4 g of silica gel using 50:1 v/v methylene chloride/acetonitrile as the eluant afforded 14 mg (28%) of 2-(S)-(3,5-bis(trifluoro-methyl)-benzyloxy)-3-(R)-phenyl-6-(R)-methyl morpholine as an oil.

Mass Spectrum (FAB): m/Z 420 (M+H, 90%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 1.39 (d, 3 H, J = 6.8), 1.92 (br s, 1 H), 2.84 and 2.95 (dAB q, 2 H, J_{AB} = 12.8, $J_{2.84}$ = 6.4, $J_{2.95}$ = 3.6), 3.93 - 4.00 (m, 1 H), 4.07 (d, 1 H, J = 2.8), 4.68 and 4.95 (AB q, 2 H, J = 13.2), 4.93 (d, 1 H, J = 2.8), 7.28 - 7.37 (m, 3 H), 7.48 - 7.52 (m, 2 H), 7.55 (s, 2 H), 7.72 (s, 1 H).

EXAMPLE 24

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine and 2-(R)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine

Substitution of 350 mg of N-(2-(S)-hydroxypropyl)-N-(2-propenyl)-(S)-phenylglycinal, 3,5-bis-(trifluoromethyl)benzyl acetal (from Example 22) for N-(2-(R)-hydroxypropyl)-N-(2-propenyl)-(R)-phenylglycinal, 3,5-bis(trifluoromethyl)benzyl acetal in an experiment similar to the preceding example afforded 50 mg of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine and 14 mg of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl morpholine.

EXAMPLE 25

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine and 2-(S)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine

Step A 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine and 2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine

The title compounds were prepared in a manner similar to Example 23, Step A. Cyclization of 300 mg (0.43 mmol) N-(2-(R)-hydroxypropyl)-N-(prop-2-

enyl)-(S)-phenylglycinal, 3,5-bis(trifluoromethyl)-benzyl acetal (from Example 23) was effected using 246 mg (1.29 mmol) of p-toluenesulfonic acid monohydrate and 5 mL of toluene. Flash chromatography on 8 g of silica gel using 20:1 v/v hexanes/ether as the eluant afforded 149 mg (75%) of the products as inseparable diastereomers.
Mass Spectrum (FAB): m/Z 460 (M+H, 65%).

Step B 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine and 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine

A solution of 150 mg (0.33 mmol) of 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine and 2-(S)-(3,5-bis-(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-4-(2-propenyl)-6-(R)-methyl morpholine (from Example 25, Step A) and 318 mg (0.32 mmol) of tris(triphenyl-phosphine)-rhodium chloride in 20 mL of 4:1 v/v acetonitrile/water was heated at reflux for 1 h. Flash chromatography on 5 g of silica gel using 9:1 v/v hexanes/ether as the eluant afforded 35 mg of the products as a mixture and 26 mg of 2-(R)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (R_f = 0.22 with 3:2 v/v hexanes/ether as the eluant). Chromatography of the mixture on 5 g of silica gel using 20:1 v/v afforded 14 mg of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (R_f = 0.14 with 3:2 v/v hexanes/ether as the eluant) and 17 mg of 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (41% total yield).

For the (2R,3S,6R) product:
Mass Spectrum (FAB): m/Z 420 (M+H, 90%)
^{1}H NMR ($CDCl_3$, 400 Mhz. ppm) 1.30 (d, 3 H, J = 6.4), 1.74 (br s, 1 H), 2.73 and 2.98 (dAB q, 2 H, J_{AB} = 11.6, $J_{2.73}$ = 10.0, $J_{2.98}$ = 2.4), 3.65 (d, 1 H, J = 7.2), 3.89 - 3.94 (m, 1 H), 4.45 (d, 1 H, J = 7.2), 4.53 and 4.90 (AB q, 2 H, J = 13.2), 7.28 - 7.38 (m, 3 H), 7.41 - 7.43 (m, 2 H), 7.45 (s, 2 H), 7.70 (s, 1 H).

For the (2S,3S,6R) product:
Mass Spectrum (FAB): m/Z 420 (M+H, 90%)
^{1}H NMR ($CDCl_3$, 400 Mhz. ppm) 1.20 (d, 3 H, J = 6.4), 2.04 (br s, 1 H), 2.84 and 3.15 (dAB q, 2 H, J_{AB} = 12.8, $J_{2.84}$ = 10.8, $J_{3.15}$ = 2.8), 4.08 (d, 1H, J = 2.8), 4.08 - 4.15 (m, 1 H), 4.53 and 4.80 (AB q, 2 H, J = 13.2), 4.79 (d, 1 H, J = 2.8), 7.28 - 7.38 (m, 5 H), 7.43 (s, 2 H), 7.70 (s, 1 H).

EXAMPLE 26

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine and 2-(R)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine

Substitution of 250 mg of N-(2-(S)-hydroxy-propyl)-N-(2-propenyl)-(S)-phenylglycinal, 3,5-bis-(trifluoromethyl)benzyl acetal (from Example 22) for N-(2-(R)-hydroxypropyl)-N-(2-propenyl)-(R)-phenyl-glycinal, 3,5-bis(trifluoromethyl)benzyl acetal in an experiment similar to the preceding example afforded 42 mg of 2-(S)-(3,5-bis(trifluoro-

methyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine and 17 mg of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl morpholine.

EXAMPLE 27

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine, 2-(S)-(3,5-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine, 2-(R or S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-3-(R)-phenyl-5-(R)-methylmorpholine, and 2-(S or R)-(3,5-Bis(trifluoromethyl) benzyloxy)-3-(R)-phenyl-5-(R)-methylmorpholine

Execution of the sequence described in Example 19 substituting (R)-2-amino-1-propanol for (R)-1-amino-2-propanol provided a mixture of 55 mg of high R_f material and 56 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide 10 mg of high R_f material (2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine and 7 mg of low R_f material (2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine. The low R_f material (after being combined with an additional 30 mg of material) was processed according to Example 23, Step A to provide 24 mg of high R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine and 18 mg of low R_f material (2-(S or R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methylmorpholine.

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 100%), 227 (50%), 192 (75%), 176 (65%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 0.98 (d, 3H, J= 6.3 Hz), 3.16-3.20 (m, 1H), 3.43-3.47 (m, 1H), 3.79 (d, 1H, J= 7.5 Hz), 3.91 (dd, 1H, J= 3.2 &11.5 Hz), 4.51 (d, 2H, J= 13.4 Hz), 4.85 (d, 1H, J= 13.2 Hz), 7.29-7.45 (m, 7H), 7.67 (s, 1H).

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 48%), 227 (35%), 192 (39%), 176 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.10 (d, 3H, J= 6.4 Hz), 3.23-3.26 (m, 1H), 3.56-3.61 (m, 2H), 4.17 (d, 1H, J= 2.3 Hz), 4.51 (d, 1H, J= 13.7 Hz), 4.71 (d, 1H, J= 2.4 Hz), 4.78 (d, 1H, J= 13.5 Hz), 7.28-7.39 (m, 7H), 7.68 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl morpholine

Mass Spectrum (FAB): m/Z 281 (35%), 221 (55%), 207 (45%), 192 (40%), 147 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.13 (d, 3H, J= 6.6 Hz), 3.10-3.14 (m, 1H), 3.66 (dd, 1H, J= 6.6 & 11.4 Hz), 3.76 (dd, 1H, J= 3.5 & 11.2 Hz), 4.04 (d, 1H, J= 4.0 Hz), 4.61 (d, 1H, J= 13.2 Hz), 4.74 (d, 1H, J= 3.9 Hz), 4.89 (d, 1H, 13.2 Hz), 7.26-7.35 (m, 3H), 7.47-7.49 (m, 2H), 7.64 (s, 1H), 7.74 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl morpholine

NMR ($CDCl_3$, 400 MHz, ppm): d 1.36 (d, 3H, J= 6.7 Hz), 3.27-3.31 (m, 1H), 3.39 (dd, 1H, J= 2.2 & 11.3 Hz), 4.16 (dd, 1H, J= 3.2 & 11.0 Hz), 4.37 (d, 1H, J= 2.3 Hz), 4.53 (d, 1H, J= 13.5 Hz), 4.75 (d, 1H, J= 2.5 Hz), 4.81 (d, 1H, 13.6 Hz), 7.26-7.35 (m, 3H), 7.26-7.43 (m, 7H), 7.68 (s, 1H).

EXAMPLE 28

2-(R or S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine, 2-(S or R)-(3,5-(-Bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine, and 2-(R)-(3,5-Bis(trifluoromethyl)benzyl-oxy)-3-(R)-phenyl-5-(S)-methylmorpholine

Execution of the sequence described in Example 19 substituting (S)-2-amino-1-propanol for (R)-1-amino-2-propanol provided a mixture of 78 mg of high R_f material and 70 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide less than 1 mg of high R_f material (2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine) and 9 mg of low R_f material (2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl morpholine. The low R_f material was processed according to Example 23, Step A to provide 20 mg of high R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine and 14 mg of low R_f material (2-(S or R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methylmorpholine.

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 60%), 227 (68%), 192 (56%), 176 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.12 (d, 3H, J= 6.6 Hz), 3.09-3.14 (m, 1H), 3.65 (dd, 1H, J= 6.6 & 11.0 Hz), 3.75 (dd, 1H, J= 3.6 & 11.1 Hz), 4.04 (d, 1H, J= 3.9 Hz), 4.61 (d, 1H, J= 13.2 Hz), 4.73 (d, 1H, J= 3.9 Hz), 4.89 (d, 1H, 13.2 Hz), 7.28-7.35 (m, 3H), 7.47 (d, 2H, 7.0 Hz), 7.64 (s, 1H), 7.74 (s, 1H).

2-(S or R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl morpholine

Mass Spectrum (FAB): m/Z 420 (M+H, 50%), 227 (45%), 192 (40%), 176 (100%).

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.36 (d, 3H, J= 6.9 Hz), 3.27-3.29 (m, 1H), 3.39 (dd, 1H, J= 2.2 & 11.1 Hz), 4.15 (dd, 1H, J= 3.3 & 11.1 Hz), 4.37 (d, 1H, J= 2.5 Hz), 4.52 (d, 1H, J= 13.3 Hz), 4.75 (d, 1H, J= 2.4 Hz), 4.81 (d, 1H, 13.5 Hz), 7.28-7.43 (m, 7H), 7.68 (s, 1H).

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-methyl morpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.10 (d, 3H, J= 6.4 Hz), 3.22-3.25 (m, 1H), 3.55-3.60 (m, 2H), 4.17 (d, 1H, J= 2.3 Hz), 4.51 (d, 1H, J= 13.5 Hz), 4.71 (d, 1H, J= 2.4 Hz), 4.77 (d, 1H, J= 13.6 Hz), 7.28-7.38 (m. 7H), 7.67 (s, 1H).

EXAMPLE 29

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine, 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine, and 2-(R or S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-3-(R)-phenyl-5-(R)-phenylmorpholine

Execution of the sequence described in Example 19 substituting (R)-2-amino-2-phenylethanol for (R)-1-amino-2-propanol provided a mixture of 62 mg of high R_f material and 52 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide 16 mg of high R_f material (2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine and 4 mg of low R_f material (2-(S)-(3,5-Bis(trifluoromethyl)benzyl-oxy)-3-(S)-phenyl-5-(R)-phenylmorpholine . The low R_f material was processed according to Example 23, Step A to provide 4 mg of product (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyl-oxy)-3-(R)-phenyl-5-(R)-phenylmorpholine.

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.62 (t, 1H, J= 10.7 & 21.5 Hz), 3.93 (d, 1H, J= 7.4 Hz), 3.99 (dd, 1H, J= 3.1 & 11.2 Hz), 4.18 (dd, 1H, J= 3.0 & 10.2 Hz), 4.46 (d, 1H, J= 7.4 Hz), 4.53 (d, 1H, J= 13.5 Hz), 4.89 (d, 1H, J= 13.3 Hz), 7.28-7.55 (m, 12H), 7.69 (s, 1H).

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.67 (dd, 1H, J= 3.5 & 11.0 Hz), 3.89 (d, 1H, J= 10.8 & 21.6 Hz), 4.25 (dd, 1H, J= 3.3 & 11.0 Hz), 4.34 (d, 1H, J= 2.2 Hz), 4.52 (d, 1H, J= 13.8 Hz), 4.78-4.87 (m, 2H), 7.28-7.51 (m, 12H), 7.69 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 4.10-4.25 (m, 2H), 4.30-4.38 (m, 1H), 4.48-4.54 (m, 1H), 4.59-4.66 (m, 1H), 4.86-5.00 (m, 2H), 7.25-7.74 (m, 13H).

EXAMPLE 30

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine, 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine, 2-(R or S)-(3,5-Bis-(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-5-(S)-phenyl-morpholine, and 2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine

Execution of the sequence described in Example 19 substituting (S)-2-amino-2-phenylethanol for (R)-1-amino-2-propanol provided a mixture of 75 mg of high R_f material and 64 mg of low R_f material. The high R_f material was processed according to Example 23, Step A above to provide 23 mg of high R_f material (2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine [L-740, 930]) and 7 mg of low R_f material (2-(R)-(3,5-Bis(trifluoro-

methyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine. The low R_f material was processed according to Example 23, Step A to provide 26 mg of higher R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine and 6 mg of lower R_f material (2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine.

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.60-3.74 (m, 1H), 3.94 (d, 1H, J= 7.6 Hz), 4.00 (dd, 1H, J= 3.2 & 11.3 Hz), 4.18-4.21 (m, 1H), 4.50-4.55 (m, 2H,), 4.89 (m, 1H), 7.26-7.55 (m, 12H), 7.69 (s, 1H).

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.68 (dd, 1H, J= 3.0 & 11.0 Hz), 3.88-3.94 (m, 1H), 4.26-4.30 (m, 1H), 4.36 (s, 1H), 4.52 (d, 1H, J= 13.5 Hz), 4.77-4.86 (m, 2H), 7.27-7.51 (m, 12H), 7.69 (s, 1H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.93-3.95 (m, 1H), 4.06-4.21 (m, 2H), 4.38-4.42 (m, 1H), 4.59-4.68 (m, 2H), 4.83-4.94 (m, 2H), 7.25-7.81 (m, 13H).

2-(R or S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-phenylmorpholine

NMR ($CDCl_3$, 400 MHz, ppm): δ 3.43-3.59 (m, 2H), 3.82 (d, 1H, J= 7.2 Hz), 4.25 (d, 1H, J= 12.5 Hz), 4.52-4.63 (m, 3H), 4.80-4.90 (br s, 1H), 7.11-7.81 (m, 13H).

EXAMPLE 31

2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine

According to the procedure given in Example 17, Step B, 98 mg (0.24 mmole) of 2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (from Example 25 above), 38 mg (0.28 mmole) of N-formyl-2-chloroacetamidrazone (from Example 17, Step A above) and 97 mg (0.7 mmole) of anhydrous potassium carbonate gave, after flash chromatography on 28 g of silica eluting with 1 L of 100:4:0.5 methylene chloride:methanol: ammonia water, a light yellow solid which after recrystallization from hexanes/methylene chloride provided 77 mg (66%) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine as a white powder.

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.17 (d, J= 6.3, 3H), 2.29 (t, J= 11.1, 1H), 2.92 (d, J= 11.1, 1H), 3.42 (d, J= 15.3, 1H), 3.58 (s, 1H), 3.88 (d, J= 15.4, 1H), 4.20-4.33 (m, 1H), 4.43 (d, 13.5, 1H), 4.71 (d, J= 2.4, 1H), 4.74 (d, J= 13.3, 1H), 7.30-7.55 (m, 7H), 7.69 (s, 1H), 7.95 (s, 1H).

EXAMPLE 32

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

A mixture of 96 mg (0.23 mmole) of 2-(S)-(3,5-bis-

(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl morpholine (from Example 25 above), 46 mg (0.28 mmole) of N-methylcarboxy-2-chloroacetamidrazone and 95 mg (0.69 mmole) of anhydrous potassium carbonate in 3 mL of dry DMF was stirred at room temperature for 20 min, at 60°C for 90 min and then at 120°C for 2 hr. The mixture was cooled to room temperature, taken up in 15 mL of ethyl acetate and was washed with 3x10 mL of water. The combined aqueous layers were back-extracted with 10 mL of ethyl acetate, the combined organic layers were washed with 10 mL of brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on 28 g of silica eluting with 1L of 100:4 methylene chloride: methanol to give 65 mg (55%) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)-methyl)-3-(S)-phenylmorpholine as a light yellow powder.

NMR ($CDCl_3$, 400 MHz, ppm): δ 1.18 (d, J= 6.2, 3H), 2.15 (t, J= 11.1, 1H), 2.89 (d, J= 14, 2H), 3.49 (d, J= 2.2, 1H), 3.61 (d, J= 14.4, 1H), 4.20-4.30 (m, 1H), 4.45 (d, J= 13.6, 1H), 4.67 (d, J= 2.5, 1H), 4.79 (d, J= 13.5, 1H), 7.25-7.50 (m, 7H), 7.62 (s, 1H), 10.07 (s, 1H), 10.35 (s, 1H).

EXAMPLE 33

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl morpholine

Step A 4-Benzyl-2-(S)-hydroxy-3-(R)-phenylmorpholine

A solution of 3.72 g (13.9 mmol) of 4-benzyl-3-(R)-phenyl-2-morpholinone, prepared from (R)-phenylglycine as described in Example 14, in 28 mL of CH_2Cl_2 was cooled in a -78°C bath under a N_2 atmosphere and 14 mL of a 1.5 M solution of DIBAL-H (21 mmol) in toluene were added. After stirring the resulting solution for 0.5 h, it was allowed to warm to -50°C and mantained at this temperature for 0.5 h. The reaction mixture was quenched by adding 10 mL of aqueous potassium sodium tartarate. The mixture was diluted with CH_2Cl_2 and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2. The CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4 and filtered. Concentration of the filtrate furnished 3.32 g (88%) of 4-benzyl-2-(S)-hydroxy-3-(R)-phenylmorpholine suitable for use in the next step.

NMR ($CDCl_3$) 2.28 (m, 1H), 2.71 (m, 1H), 2.91 (d, J = 13 Hz, 1H), 3.09 (d, J = 6 Hz, 1H), 3.69 (d, J = 13 Hz, 1H), 3.82 (td, J = 10 Hz and 2 Hz, 1H), 3.91 (d, J = 10 Hz, 1H), 4.73 (t, J = 6 Hz, 1H), 7.2-7.52 (m, 10H).

Step B 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(R)-phenylmorpholine

To a suspension of 0.592 g (14.8 mmol) of NaH in 30 mL of dry THF at 0 °C was added 3.32 g (12.3 mmol) of 4-benzyl-2-(S)-hydroxy-3-(R)-phenylmorpholine prepared in step A. After 15 min 0.915 g of tetrabutylammonium iodide (2.47 mmol) and 2.4 mL (13 mmol) of 3,5-bis(trifluoromethyl)benzyl bromide

were added. The resulting mixture was stirred at ice-bath temperature for 1 h, then poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate (EtOAc). The organic layers were combined, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the resiue was chromatographed on a Waters Prep500 HPLC system using 50% EtOAc/Hexane to isolate 3.6 g (59%) of 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine.

^1H NMR ($CDCl_3$) 2.3(td, J = 11 Hz and 3 Hz, 1H), 2.71 (d, J = 11 Hz, 1H), 2.90 (d, J = 13 Hz, 1H), 3.22 (d, J = 7.3 Hz, 1H), 3.75 (m, 2H), 3.93 (m, 1H), 4.43 (d, J = 13 Hz, 1H), 4.45 (d, J = 7.3 Hz, 1H), 4.82 (d, J = 13 Hz, 1 H), 7.19-7.5 (m, 12H), 7.67 (s, 1H).

Step C 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

A solution of 3.6 g (7.27 mmol) of 4-benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine in 100 mL of ethanol and 5 mL of water, containing 0.72 g of 10% Pd/C was hydrogenated on a Parr apparatus for 36 h. The catalyst was filtered and thoroughly washed with EtOAc. The filtrate was concentrated and the residue was partitioned between water and EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography using a gradient of 10-60 % EtOAc/hexane to isolate 2.05 g (70%) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine.

^1H NMR ($CDCl_3$) 1.92 (br s, 1H), 2.91 (m, 1H), 3.05

(td, J =11Hz and 3 Hz, 1H), 3.68 (d, J = 7 Hz, 1H), 3.81 (td, J = 11 Hz and 3 Hz, 1H), 4.01 (m, 1H), 4.44 (d, J = 7 Hz), 4.5 (d, J = 13 Hz, 1H), 4.85 (d, J = 13 Hz, 1 H), 7.28-7.42 (m, 7H), 7.67 (s, 1H).

EXAMPLE 34

4-(3-(1,2,4-Triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 17, step B employing the product of Example 33, step C as a starting material.

^{1}H NMR ($CDCl_3$) 1.75 (br s, 1 H), 2.61 (td, J =12 Hz and 2 Hz, 1H), 2.83 (d, J = 12 Hz, 1H), 3.33 (d, J = 7 Hz, 1H), 3.48 (d, J = 15 Hz, 1H), 3.78 (d, J = 15 Hz, 1H), 3.85 (m, 1H), 3.99 (m, 1H), 4.44 (d, J = 13 Hz, 1 H), 4.49 (d, J = 7Hz, 1H), 4.81 (d, J = 13 Hz, 1H), 7.23-7.45 (m, 7H), 7.67 (s, 1H), 7.96 (s,1H).

EXAMPLE 35

4-(3-(5-Oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl) benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 18, steps B & C employing the product of Example 33, step C as a starting material.

EXAMPLE 36

4-(2-(Imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine

A solution of 101 mg (0.25 mmol) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (Example 15), 98 mg (1.0 mmol) of imidazole-2-carboxaldehyde, and 5 drops of glacial acetic acid in 3 ml of methanol was treated with 1.5 ml of 1M sodium cyanoborohydride solution in THF. After 16 hr, the reaction was quenched with 5 ml of saturated aqueous sodium bicarbonate solution and partitioned between 40 ml of ethyl acetate and 20 ml of water. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 8 g of silica gel using 50:1:0.1 methylene chloride/methanol/amonium hydroxide as the eluent afforded 54 mg (44% yield) of the title compound as a white solid.
^{1}H NMR ($CDCl_3$) 2.60 (dt, J = 3.2 Hz and 12.4 Hz, 1H), 2.85 (d, J =12.4 Hz, 1H), 3.28 (d, J = 14.4 Hz, 1H), 3.59 (d, J =2.8 Hz, 1H), 3.66 (dd, J =2.0, 11.6 Hz, 1H), 3.84 (d, J =14.4 Hz, 1H), 3.94 (app s, 2H), 4.14 (dt, J = 2.0, 12.0 Hz, 1H), 4.43 (d, J = 13.6 Hz, 1H), 4.71 (d, J = 2.8 Hz, 1H), 4.78 (d, J = 13.6 Hz, 1H), 6.99 (app s, 2H), 7.25-7.48 (m, 6H), 7.72 (s, 1H). Mass spectrum (FAB): m/z 486 (100%, M+H)

EXAMPLE 37

4-(2-(Imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 36 employing appropriate starting materials.

^{1}H NMR ($CDCl_3$) 2.53 (td, J = 11 Hz and 3 Hz, 1H),

2.74 (d, J =12 Hz, 1H), 3.23 (d, J = 7Hz, 1H), 3.32 (d, J =15 Hz, 1H), 3.66 (d, J =15 Hz, 1H), 3.77 (td, J =11 Hz and 2 Hz, 1H), 3.99 (m, 1H), 4.44 (m, 2H), 4.8 (d, J = 13 Hz, 1H), 6.94 (s, 2H), 7.2-7.45 (m, 7H), 7.67 (s, 1H).

EXAMPLE 38

4-(5-(Imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 36 employing appropriate starting materials.

^{1}H NMR ($CDCl_3$) 2.47 (td, J = 12 Hz and 3 Hz, 1H), 2.83 (d, J = 12 Hz, 1H), 3.2 (m, 2H), 3.61 (d, J =14 Hz, 1H), 3.79 (td, J =12 Hz and 2 Hz, 1H), 3.96 (m, 1H), 4.44 (m, 2H), 4.80 (d, J =13 Hz, 1H), 6.81 (s, 1H), 7.28-7.45 (m, 7H), 7.60 (s, 1H), 7.66 (s, 1H).

EXAMPLE 39

4-(Aminocarbonylmethyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine

The title compound was prepared by the procedure of Example 15 employing appropriate starting materials.

^{1}H NMR ($CDCl_3$) 2.54 (td, J = 11 Hz and 2 Hz, 1H), 2.64 (d, J = 17 Hz, 1H), 2.93 (d, J 12 Hz, 1H), 3.14 (d, J = 17 Hz, 1H), 3.27 (d, J =7 Hz, 1H), 3.83 (td, J = 11 Hz and 2 Hz, 1H), 4.05 (m, 1H), 4.46 (m, 2H), 4.81 (d, J =13 Hz, 1H), 5.62 (br s, 1H), 6.80 (br s, 1H), 7.28-7.32 (m, 7H), 7.67 (s, 1H).

EXAMPLES 40-43

4-(3-(1,2,4-Triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine, 4-(3-(5-Oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine, 4-(2-(Imidazolo)methyl)-2-(3-(tert-butyl)-5-methyl-benzyloxy)-3-phenyl-morpholine, 4-(4-(Imidazolo)-methyl)-2-(3-(tert-butyl)-5-methyl-benzyloxy)-3-phenyl-morpholine

The title compounds are each prepared by the procedures of Examples 15, 17 & 18 employing appropriately substituted starting materials and reagents.

EXAMPLE 44

2-(S)-(3,5-Dichlorobenzyloxy)-3-(S)-phenylmorpholine

Step A: 3,5-Dichlorobenzyl alcohol, trifluoromethane-sulfonate ester

A solution of 6.09 g (34.4 mmole) of 3,5-dichlorobenzyl alcohol and 8.48 g (41.3 mmole) of 2,6-di-t-butyl-4-methylpyridine in 280 mL of dry carbon tetrachloride under a nitrogen atmosphere was treated with 5.95 mL (35.4 mmole) of trifluoromethane-sulfonic anhydride at room temperature. A white precipitate formed shortly after the addition of the anhydride. After 90 min, the slurry was filtered under nitrogen with a Schlenk filter, and the filtrate was concentrated in vacuo. The residue,

which was a two-phase oil, was dissolved under nitrogen in 60 mL of dry toluene. The resulting solution was used immediately in Step B below.

Step B: 4-Benzyl-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine

A solution of 5.11 g (19.1 mmole) of N-benzyl-3-(S)-phenylmorpholin-2-one (from Example 14) in 100 mL of dry THF was cooled to -75°C under nitrogen and was treated dropwise with 20.5 mL (20.5 mmole) of a 1M solution of lithium tri(sec-butyl)-borohydride (L-Selectride®) in THF. After stirring the solution at -75°C for 30 min, a solution of 3,5-dichlorobenzyl alcohol, trifluoromethanesulfonate ester in toluene (from Example 44, Step A) was added by cannula so that the internal temperature was maintained below -60°C. The resulting solution was stirred between -38°C and -50°C for 9 hr, and was then treated with 14 mL of aqueous ammonia and stored at -20°C for 12 hours. The solution was then poured into a mixture of 50 mL of ethyl acetate and 100 mL of water, and the layers were separated. The aqueous phase was extracted with 2x100 mL of ethyl acetate, each extract was washed with brine, the combined organic layers were dried over sodium sulfate, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on 235 g of silica eluting with 1.5 L of 100:2 hexanes:ethyl acetate, then 1.5 L of 100:3 hexanes:ethyl acetate and then 1.9 L of 100:5 hexanes:ethyl acetate to give 4.4 g (54%) of an oil, which by ^1H NMR is a 8:1 mixture of cis:trans morpholines.

Mass Spectrum (FAB): m/Z 430,428,426 (M+H, ~60%), 268 (M-$ArCH_2$, 100%), 252 (M-$ArCH_2O$, 75%), 222(20%), 159 (45%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ major (cis) isomer: 2.32 (td, J= 12, 3.6, 1H), 2.84 (app t, J= 13, 2H), 3.52 (d, J= 2.6, 1H), 3.55 (dq, J= 11.3, 1.6, 1H), 3.91 (d, J= 13.3, 1H), 4.12 (td, J= 11.6, 2.4, 1H), 4.29 (d, J= 13.6, 1H), 4.59 (d, J= 2.9, 1H), 4.60 (d, J= 13.6), 6.70 (s, 2H), 7.13 (t, J= 1.9, 1H), 7.2-7.6 (m, 8H), 7.53 (br d, 2H).

Step C: 2-(S)-(3,5-Dichlorobenzyloxy)-3-(S)-phenyl-morpholine

A solution of 0.33 g (0.77 mmole) of 4-benzyl-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenyl-morpholine (from Example 44, Step B) and 0.22 g (1.54 mmole) of 1-chloroethyl chloroformate in 4.5 mL of 1,2-dichloroethane was placed in a pressure vial which was lowered into an oil bath which was heated to 110°C. After stirring for 60 hr the solution was cooled and concentrated in vacuo. The residue was dissolved in 7 mL of methanol and the resulting solution was heated at reflux for 30 min. The mixture was cooled and treated with several drops of concentrated aqueous ammonia and the solution was concentrated. The residue was partly purified by flash chromatography on 67 g of silica eluting with 1.5 L of 100:1 methylene chloride: methanol, and the rich cuts were purified by flash chormatography on 32 g of silica eluting with 50:50 hexanes: ethyl acetate

and then 50:50:5 hexanes:ethyl acetate:methanol to give 0.051 g (20%) of an oil, which by ^{1}H NMR was pure cis morpholine.

Mass Spectrum (FAB): m/Z 468,466,464 (max 8%)), 338,340 (M+H, 25%), 178 (20%), 162 (100%), 132 (20%),.

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.89 (br s, 1H), 3.08 (dd, J= 12.5, 2.9, 1H), 3.23 (td, J= 12.2, 3.6, 1H), 3.59 (dd, J= 11.3, 2.5, 1H), 4.03 (td, J= 11.7, 3, 1H), 4.09 (d, J= 2.4, 1H), 4.37 (d, J= 13.5, 1H), 4.62 (d, J= 13.3, 1H), 4.67 (d, J= 2.5, 1H), 6.72 (d, J= 1.8, 2H), 7.14 (t, J= 1.8, 1H), 7.25-7.40 (m, 5H).

EXAMPLE 45

2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

Step A: N-Methylcarboxy-2-chloroacetamidrazone

A solution of 5.0 g (66.2 mmol) of chloroacetonitrile in 35 mL of dry methanol was cooled to 0°C and was treated with 0.105 g (1.9 mmol) of sodium methoxide. The ice-bath was removed and the mixture was alowed to stir at room temperature for 30 minutes. To the reaction was then added 0.110 mL (1.9 mmol) of acetic acid and then 5.8 g (64.9 mmol) of methyl hydrazinecarboxylate. After stirring 30 minutes at room temperature, the suspension was concentrated in vacuo, and placed on the high-vac line overnight, to give 10.5 g (98%) of a yellow powder, a portion of which was employed in Step C below.

Step B: 4-(2-(N-Methylcarboxy-acetamidrazono)-2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine

A solution of 0.050 g (0.15 mmol) of 2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenylmorpholine (from Example 44, Step C), 0.034 g (0.21 mmol) of N-methylcarboxy-2-chloroacteamidrazone (from Step A), and 0.044 mL (0.25 mmol) N,N-diisopropylethylamine in 1 mL of acetonitrile was stirred at room temperature for 3 hours. The mixture was partitioned between 20 mL of methylene chloride and 10 mL of water. The layers were separated, the organic layer was dried over sodium sulfate and was then concentrated in vacuo. The residue was purified by flash chromatography on 35 g of silica eluting with 1L of 50:1: methylene chloride/methanol then 500 mL of 25:1:0.05 methylene chloride:methanol:aqueous ammonia to give 70 mg (~100%) of the product as a white solid.

Mass Spectrum (FAB): m/Z 469 (M+H, 60%), 467 (M+H, 100%),291 (40%), 160 (20%), 158 (25%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.48 (td, J= 3.5, 12.2, 1H), 2.53 (d, J= 14.6, 1H), 2.90 (d, J= 11.8, 1H), 3.37 (d, J= 14.6, 1H), 3.52 (d, J= 2.8), 1H), 3.62 (dm, J= 11.4, 1H), 3.75 (s, 3H), 4.14 (td, J= 2.2, 11.8, 1H), 4.28 (d, J= 13.5, 1H), 4.58 (d, J= 13.6), 4.60 (d, J= 2.8, 1H), 5.45 (br s, 2H), 6.74 (d, J= 1.9, 2H), 7.15 (t, J= 1.9, 1H), 7.30-7.46 (m, 6H).

Step C: 2-(S)-(3,5-Dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine

A solution of 0.069 g (0.15 mmol) of 4-(2-(N-methylcarboxy-acetamidrazono)-2-(S)-(3,5-dichloro-benzyloxy)-3-(S)-phenylmorpholine (from Step B) in 6 mL of xylenes was heated at reflux for 2 hours. The solution was cooled and concentrated in vacuo. The residue was purified by flash chromatography on 35 g of silica gel eluting with 500 mL of 50:1:0.1 methylene chloride/methanol/aqueous ammonia then 500 mL of 20:1:0.1 methylene chloride/methanol/aqueous ammonia to give 56 mg (88%) of the product as a white powder.

Mass Spectrum (FAB): m/Z 437 (M+H, 65%), 435 (M+H, 100%), 259 (85%), 161 (55%).

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.53 (t, J= 11.7, 3.6, 1H), 2.88 (d,J= 11.6, 1H), 2.96 (d, J= 14.3, 1H), 3.54 (d, J= 2.6, 1H), 3.63 (dd, J= 11.6, 1.9, 1H), 3.68 (d, J= 14.6, 1H), 4.16 (t, J= 11.7, 2.2, 1H), 4.30 (d, J= 13.6), 4.58 (d, J= 2.7, 1H), 4.67 (d, J= 13.6, 1H), 6.65 (d, J= 1.8, 2H), 7.07 (t, J= 1.9, 1H), 7.29-7.44 (m, 5H), 10.25 (br s, 1H), 10.75 (br s, 1H).

EXAMPLE 46

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylmethyl)-3-(S)-phenylmorpholine

A solution of 300 mg (0.74 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (from Example 15, Step C) and 0.35 mL (2.0 mmole) of DIEA in 5 mL of acetonitrile was treated with 0.19 mL (2.0 mmole) of methyl bromoacetate and the mixture was stirred for 16 hr at room temperature. The solution was then concentrated in vacuo and the residue partitioned between 30 mL of ether and 15 mL of 0.5 N aqueous $KHSO_4$. The layers were separated and the organic phase was washed with 10 mL of brine and dried over magnesium sulfate. Following filtration, the organic phase was concentrated in vacuo and the residue purified by flash chromatography on 20 g of silica eluting with 80:20 hexanes:ether to give 351 mg (99%) of the product. $[\alpha]_D$ = +147.3° (c= 1.6, $CHCl_3$).

Mass Spectrum (FAB): m/Z 478 (M+H, 40%), 477 (65%), 418 (50%), 250 (95%), 234 (90%), 227 (100%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 3.02 (br d, 2H), 3.13 (d, J= 16.9, 1H), 3.36 (d, J= 16.8), 3.62 (s, 3H), 3.69 (dt, J= 11.7, 2.2, 1H), 4.03 (br s, 1H), 4.23-4.32 (m, 1H), 4.44 (d, J= 13.3, 1H), 4.68, (d, J= 2.6, 1H), 4.81 (d, J= 13.5, 1H), 7.30-7.38 (m, 3H), 7.4-7.5 (m, 3H), 7.70 (s, 1H).

Analysis:

Calcd for $C_{22}H_{21}F_6NO_4$: C-55.35 H-4.43 N-2.93 F-23.88

Found: C-55.09 H-4.43 N-2.83 F-24.05

EXAMPLE 47

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine

A solution of 0.016 g (0.034 mmole) of 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylmethyl)-3-(S)-phenylmorpholine (from Example 46) in 2 mL of THF and 0.5 mL of water was treated with 0.027 mL (0.067 mmole) of 2.5 N aqueous sodium hydroxide and the mixture was stirred at room temperature for 5 hr. The mixture was treated with 2 drops of 2N aqueous HCl and 3 mL of water and the solution was extracted with 15 mL of 1:1 hexanes:ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chormatography on 13 g of silica eluting with 250 mL of 100:3:0.1 methylene chloride:methanol:acetic acid then 100 mL of 50:2:0.1 methylene chloride: methanol:acetic acid to give 0.014 g (90%) of an oil.

Mass Spectrum (FAB): m/Z 464 (M+H, 90%), 420 ($M-CO_2$, 10%), 227 ($ArCH_2$, 35%), 220 ($M-OCH_2Ar$, 100%), 161 (20%).

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.9 (app d, 2H), 3.03 (d, 1H), 3.33 (d, 1H), 3.72 (d, 1H), 3.90 (d, 1H), 4.25 (t, 1H), 4.44 (d, 1H), 4.71 (d, 1H), 4.79 (d, 1H), 7.3-7.4 (m, 5H), 7.44 (s, 2H), 7.71 (s, 1H).

EXAMPLE 48

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-((2-aminoethyl)aminocarbonylmethyl)-3-(S)-phenylmorpholine hydrochloride

A solution of 54 mg (0.11 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine (from Example 46) and 0.15 mL of ethylenediamine (2.3 mmole) in 1 mL of methanol was stirred at 55°C for 48 hr. The mixture was concentrated and the residue purified by flash chromatography on 16 g of silica eluting with 500 mL of 50:4:0.1 methylene chloride:methanol: aqueous ammonia to provide 57 mg(100%) of an oil. The oil was dissolved in ether and was treated with ether saturated with gaseous HCl. After concentration in vacuo, 58 mg (95%) of a rigid oil was obtained.

Mass Spectrum (FAB; free base): m/Z 506 (M+H, 100%), 418 (15%), 262(35%), 227 (30%), 173 (40%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.56 (d, J= 15.5, 1H), 2.59 (td, J= 12.0, 3.6, 1H), 2.82 (t, J= 6.5, 2H), 2.96 (d, J= 11.8, 1H), 3.21 (d, J= 15.8, 1H), 3.25-3.40 (m, 2H), 3.65 (d, J= 2.6, 1H), 3.67 (app dt, J= 11.4, ~2, 1H), 4.18 (td, J= 11.8, 2.6, 1H), 4.33 (d, J= 13.5, 1H),4.69 (d, J= 2.7, 1H), 4.79 (d, J= 13.5, 1H), 7.25-7.40 (m, 5H), 7.46 (s, 2H), 7.59 (br t, 1H), 7.71 (s, 1H).

EXAMPLE 49

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-((3-amino-propyl)amino carbonylmethyl)-3-(S)-phenylmorpholine hydrochloride

A solution of 59 mg (0.12 mmole) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine (from Example 46) and 0.21 mL of 1,3-propylenediamine (2.5 mmole) in 1 mL of methanol was stirred at 55°C for 72 hr. The mixture was concentrated and the residue purified by flash chromatography on 16 g of silica eluting with 500 mL of 10:1:0.05 methylene chloride:methanol: aqueous ammonia to provide 56 mg (88%) of an oil. The oil was dissolved in methylene chloride and was treated with methylene chloride saturated with gaseous HCl. After concentration in vacuo, a white paste was obtained.

Mass Spectrum (FAB; free base): m/Z 520 (M+H, 100%), 418 (10%), 276(30%), 227 (20%), 174 (30%)

^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.64 (pentet, J= 6.6, 2H), 2.53 (d, J= 15.5, 1H), 2.58 (td, J= 12.0, 3.6, 1H), 2.73 (t, J= 6.5, 2H), 2.92 (d, J= 11.8, 1H), 3.19 (d, J= 15.8, 1H), 3.25-3.40 (m, 2H), 3.62 (d, J= 2.6, 1H), 3.65 (app dt, J= 11.4, ~2, 1H), 4.16 (td, J= 11.8, 2.6, 1H), 4.41 (d, J= 13.5, 1H),4.68 (d, J= 2.7, 1H), 4.79 (d, J= 13.5, 1H), 7.25-7.40 (m, 5H), 7.45 (s, 2H), 7.57 (br t, 1H), 7.70 (s, 1H).

EXAMPLE 50

4-benzyl-5-(S),6-(R)-dimethyl-3-(S)-phenylmorpholinone and 4-benzyl-5-(R),6-(S)-dimethyl-3-(S)-phenylmorpholinone

To a suspension of 1.7 g (7.0 mmole) of N-benzyl-(S)-phenylglycine (Example 13) in 15 ml of methylene chloride at 0°C was added 6.9 ml (13.9 mmole) of trimethylaluminum (2.0 M in toluene). After one hour at 0°C, 0.625 ml (7.0 mmole) of (+/-)-trans-2,3-epoxy butane (dissolved in 2.0 ml of methylene chloride) was added dropwise and then allowed to stir at 22°C for 16 hours. The reaction was then transferred to another flask containing 30 ml of 1:1 hexane:methylene chloride and 30 ml of 1M potassium sodium tartrate and stirred at 22°C for 2 hours. The layers were separated, and the aqueous layer was extracted with methylene chloride (3 x 100 ml). The combined organic layers were washed with 25 ml of a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo.

The crude alcohol was dissolved in 25 ml of toluene, treated with 93 mg (0.49 mmole) of p-toluenesulfonic acid and heated at 50°C for 20 hours. The reaction was then cooled and concentrated in vacuo . The residue was partitioned between 15 ml of diethyl ether and 10 ml of saturated sodium bicarbonate. The layers were separated, and the organic layer was washed with water (3 x 10 ml). The combined organic layers were washed with 25 ml of a saturated sodium

chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography on 145 g of silica gel using 1:4 v/v ethyl acetate/ hexane as the eluant afforded 567 mg of the high R_f lactone (Isomer A) and 388 mg of the low R_f lactone (Isomer B).

^{1}H-NMR (400 MHz, $CDCl_3$) δ Isomer A: 1.04 (d, 3H, J = 8.0 Hz), 1.24 (d, 3H, J = 8.0 Hz), 2.92 (br qd, 1H), 3.41 (d, 1H, J = 16.0 Hz), 3.62 (d, 1H, J = 16.0 Hz), 4.38 (s, 1H), 4.96 (br qd, 1H), 7.20-7.42 (m, 8H), 7.58-7.64 (m, 2H); Isomer B: 1.04 (d, 3H, J = 10.0 Hz), 1.39 (d, 3H, J = 10.0 Hz), 3.06 (br qd, 1H), 3.53 (d, 1H, J = 16.0 Hz), 3.81 (d, 1H, J = 16.0 Hz), 4.33 (s, 1H), 4.67 (br qd, 1H), 7.18-7.50 (m, 10H).

Mass Spectrum (FAB): m/z Isomer A: 296 (M+H, 100%), 294 (50%); Isomer B: 296 (M+H, 100%), 294 (50%).

EXAMPLE 51

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

Step A: 4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)-benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step B, 251 mg (0.85 mmole) of Isomer A from Example 50 (4-benzyl-[5-(S),6-(R) or 5-(R)-6-(S)-dimethyl]-3-(S)-phenylmorpholinone) provided 238 mg (53%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.6 Hz), 2.61 (qd, 1H, J = 2.2 & 6.6 Hz), 3.26 (d, 1H, J = 13.9 Hz), 3.55 (d, 1H, J = 13.9 Hz), 3.63 (d, 1H, J = 7.6 Hz), 4.01 (qd, 1H, J = 2.3 & 6.6 Hz), 4.44 (d, 1H, J = 13.1 Hz), 4.53 (d, 1H, J = 7.7 Hz), 4.71 (s, 1H), 4.85 (d, 1H, J = 13.2 Hz), 7.20-7.35 (m, 9H), 7.46-7.48 (m, 2H), 7.67 (s, 1H), 7.81 (s, 1H).

Mass Spectrum (FAB): m/z 523 (M+H, 100%), 296 (95%), 280 (40%), 227 (50%).

Step B: 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step C, 260 mg of starting material from Step A [derived from Isomer A in Example 50 (4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone)] provided 122 mg (57%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (d, 3H, J = 6.5 Hz), 1.27 (d, 3H, J = 6.7 Hz), 2.97 (qd, 1H, J = 2.9 & 6.9 Hz), 3.96 (d, 1H, J = 7.7 Hz), 4.08-4.11 (m, 2H), 4.39 (d, 1H, J = 7.7 Hz), 4.50 (d, 1H, J = 13.3 Hz), 4.88 (d, 1H, J = 13.2 Hz), 7.27-7.33 (m, 3H), 7.40-7.42 (m, 4H), 7.67 (s, 1H).

Mass Spectrum (FAB): m/z 434 (M+H, 45%), 227 (35%), 206 (40%), 190 (100%).

EXAMPLE 52

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

Step A: 4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)-benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step B, 449 mg (1.52 mmole) of Isomer B from Example 50 (4-benzyl-[5-(R),6-(S) or 5-(S)-6-(R)-dimethyl]-3-(S)-phenylmorpholinone) provided 400 mg (51%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 6.8 Hz), 1.37 (d, 3H, J = 6.6 Hz), 2.86-2.89 (br qd, 1H), 3.47 (d, 1H, J = 15.0 Hz), 3.82-3.85 (m, 2H), 3.99-4.02 (br qd, 1H), 4.45 (d, 1H, J = 13.6 Hz), 4.81 (d, 1H, J = 2.0 Hz), 4.87 (d, 1H, J = 13.5 Hz), 7.17-7.83 (m, 13H).

Step B: 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 15, Step C, 400 mg of starting material from Step A [derived from Isomer B in Example 50 (4-Benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone)] provided 230 mg (69%) of the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, J = 6.7 Hz), 1.38 (d, 3H, J = 7.0 Hz), 3.41-3.45 (br qd, 1H), 3.85-3.89 (br qd, 1H), 4.16 (d, 1H, J = 2.9 Hz), 4.49 (d, 1H, J = 13.6 Hz), 4.71 (d, 1H, J = 2.9 Hz), 4.82 (d, 1H, J = 13.6 Hz), 7.25-7.36 (m, 7H), 7.66 (s, 1H).

Mass Spectrum (FAB): m/z 434 (M+H, 35%), 227 (40%), 206 (40%), 190 (100%).

EXAMPLE 53

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

A mixture of 62 mg (0.14 mmole) of 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone (from Example 51, Step B), 62 mg (0.45 mmole) of anhydrous potassium carbonate and 26 mg (0.19 mmole) of N-formyl-2-chloroacetamidrazone (from Example 17, Step A) in 2.0 ml of N,N-dimethylformamide was heated to 60°C for 2 hours and then 118°C for 1.5 hours. The mixture was then allowed to cool to room temperature and then quenched with 5 mls of water and diluted with 15 mls of ethyl acetate. The layers were separated and the organic layer was washed with ethyl acetate (2 x 10 mls). The combined organic layers were washed with 10 mls of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography on 42 g

of silica gel using 95:5 v/v methylene chloride/ methanol as the eluant afforded 42 mg (57%) of a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 3H, J = 6.5 Hz), 1.19 (d, 3H, J = 6.5 Hz), 2.65 (qd, 1H, J = 1.9 & 6.5 Hz), 3.58 (d, 1H, J = 15.5 Hz), 3.65 (d, 1H, J = 7.7 Hz), 3.75 (d, 1H, J = 15.4 Hz), 4.06 (qd, 1H, J = 2.2 & 6.6 Hz), 4.45 (d, 1H, J = 13.2 Hz), 4.54 (d, 1H, J = 7.7 Hz), 4.84 (d, 1H, J = 13.2 Hz), 7.28-7.37 (m, 7H), 7.67 (s, 1H), 7.89 (s, 1H).

Mass Spectrum (FAB): m/z 516 (M+H, 52%), 287 (28%), 271 (100%), 227 (40%), 202 (38%).

EXAMPLE 54

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo) methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone

A solution of 96 mg (0.22 mmole) of 2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone (from Example 51, Step B), 92 mg (0.66 mmole) of potassium carbonate and 48 mg (0.29 mmole) of N-methylcarboxy-2-chloroacetamidrazone (from Example 18, Step A) in 4 mL of DMF was heated at 60°C for 1.5 hr and at 120°C for 3.5 hr. The mixture was cooled to room temperature and was partitioned between 15 mL of water and 25 mL of ethyl acetate. The aqueous layer

was extracted with 3x10 mL of ethyl acetate, the combined organic layers were washed with 10 mL of brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was partly purified by flash chromatography on 42 g of silica gel using 2L of 98:2 v/v methylene chloride/ methanol as the eluant and the rich cuts were purified under the same conditions to give 38 mg (33%) of a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, J = 6.5 Hz), 1.20 (d, 3H, J = 6.6 Hz), 2.64 (qd, 1H, J = 2.4 & 6.6 Hz), 3.33 (s, 1H), 3.56 (d, 1H, J = 7.6 Hz), 4.11 (qd, 1H, J = 2.4 & 6.6 Hz), 4.41 (d, 1H, J = 13.2 Hz), 4.57 (d, 1H, J = 7.7 Hz), 4.82 (d, 1H, J = 13.2 Hz), 7.25-7.30 (m, 5H), 7.40 (d, 2H, J = 5.7 Hz), 7.65 (s, 1H), 9.46 (s, 1H), 10.51 (s, 1H).

Mass Spectrum (FAB): m/z 531 (M+H, 98%), 287 (100%), 227 (80%), 189 (65%).

EXAMPLE 55

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 53, 75 mg (0.17 mmole) of 2-(S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone (from Example 52, Step B) provided, after flash chromatography on 73 g of

silica gel using 98:2 v/v methylene chloride/ methanol as the eluant , 46 mg (52%) of a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 (d, 3H, J = 6.6 Hz), 1.46 (d, 3H, J = 6.7 Hz), 3.05-3.08 (m, 1H), 3.74-3.81 (m, 2H), 3.91-3.95 (m, 2H), 4.41 (d, 1H, J = 13.2 Hz), 4.69 (d, 1H, J = 3.2 Hz), 4.82 (d, 1H, J = 13.5 Hz), 7.31-7.35 (m, 5H), 7.43-7.45 (m, 2H), 7.68 (s, 1H), 7.91 (s, 1H).

Mass Spectrum (EI): m/z 432 (36%), 287 (60%), 270 (65%), 227 (30%), 187 (48%), 83 (100%).

EXAMPLE 56

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo) methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone

According to the procedure in Example 54, 86 mg (0.2 mmole) of 2-(S)-(3,5-Bis(trifluoromethyl)-benzyloxy)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone (from Example 47, Step B) provided, after flash chromatography on 73 g of silica gel using 95:5 v/v methylene chloride/ methanol as the eluant, 32 mg (30%) of a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 6.7 Hz), 1.40 (d, 3H, J = 6.8 Hz), 3.00 (qd, 1H, J = 3.8 & 6.8 Hz), 3.44 (d, 1H, J = 16.1 Hz), 3.63 (d, 1H, J = 16.0 Hz), 3.82 (d, 1H, J = 3.3 Hz), 3.95 (qd, 1H, J = 3.7

& 6.7 Hz), 4.43 (d, 1H, J = 13.5 Hz), 4.73 (d, 1H, J = 3.3 Hz), 4.84 (d, 1H, J = 13.6 Hz), 7.28-7.47 (m, 7H), 7.68 (s, 1H), 9.52 (d, 2H).

Mass Spectrum (FAB): m/z 531 (M+H, 100%), 287 (55%), 227 (25%), 147 (50%).

EXAMPLE 57

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(2-(1-(4-benzyl)piperidino) ethyl)-3-(S)-phenylmorpholine

To a solution of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine (50 mg, 0.12 mmol) and 4-benzyl-1-(2-chloroethyl)piperidine hydrochloride (50 mg, 0.18 mmol) in acetonitrile (0.5 mL) was added diisopropylethylamine (0.065 mL, 0.36 mmol) at room temperature. After 60 hours, TLC (5% MeOH/2% Et_3N/93% EtOAc) indicated that the reaction was only partially complete. The reaction was diluted with methylene chloride and washed with water, then brine, dried over sodium sulfate and evaporated. Prep TLC (5% MeOH/2% Et_3N/93% EtOAc) afforded 36 mg (50%) of the title compound as an oil.

^1H-NMR (400 MHz, $CDCl_3$) δ 1.1-1.4 (m, 2 H), 1.4-1.65 (2 m, 4 H), 1.65-2.05 (m, 3 H), 2.05-2.3 (m, 1H), 2.35-2.5 (m and d, J = 7 Hz, 3 H), 2.55 (br t, J = 11 Hz, 1 H), 2.65-2.8 (m, 2 H), 3.09 (d, J = 11 Hz, 1 H), 3.50 (d, J = 2.5 Hz, 1 H), 3.66 (dd, J = 2 and 11 Hz, 1 H), 4.15 (dt, J = 2 and 12 Hz, 1 H), 4.38 and

4.75 (AB q, J = 13 Hz, 2 H), 4.61 (d, J = 2.5 Hz, 1 H), 7.06 (d, J = 7 Hz, 2 H), 7.15 (t, J = 7 Hz, 1 H), 7.2-7.35 (m, 5 H), 7.36 (m, 4 H), 7.75 (s, 1H).

EXAMPLE 58

(S)-(4-Fluorophenyl)glycine

Step A: 3-(4-Fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.09 g (33.0 mmol) of 4-fluorophenylacetic acid in 100 mL of anhydrous ether. The solution was cooled to -10°C and treated with 5.60 mL (40.0 mmol) of triethylamine followed by 4.30 mL (35.0 mmol) of trimethylacetyl chloride. A white precipitate formed immediately. The resulting mixture was stirred at -10°C for 40 minutes, then cooled to -78°C.

An oven-dried, 250 mL round bottom flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.31 g (30.0 mmol) of 4-(S)-benzyl-2-oxazolidinone in 40 mL of dry THF. The solution was stirred in a dry ice/acetone bath for 10 minutes, then 18.8 mL of 1.6 M n-butyllithium solution in hexanes was slowly added. After 10 minutes, the lithiated oxazolidinone solution was added, via cannula, to the mixture in the 3-necked flask. The cooling bath was removed

from the resulting mixture and the temperature was allowed to rise to 0°C. The reaction was quenched with 100 mL of saturated aqueous ammonium chloride solution, transferred to a 1 L flask, and the ether and THF were removed in vacuo. The concentrated mixture was partitioned between 300 mL of methylene chloride and 50 mL of water and the layers were separated. The organic layer was washed with 200 mL of 2 N aqueous hydrochloric acid solution, 300 mL of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and concentrated in vacuo. Flash chromatography on 400 g of silica gel using 3:2 v/v hexanes/ether as the eluant afforded 8.95 g of an oil that slowly solidified on standing. Recrystallization from 10:1 hexanes/ether afforded 7.89 g (83%) of the title compound as a white solid, mp 64-66°C.

Mass Spectrum (FAB): m/Z 314 (M+H, 100%), 177 ($M-ArCH_2CO+H$, 85%).

^1H-NMR (400 MHz, $CDCl_3$): δ 2.76 (dd, 1 H, J = 13.2, 9.2), 3.26 (dd, J = 13.2, 3.2), 4.16-4.34 (m, 4 H), 4.65-4.70 (m, 1 H), 7.02-7.33 (m, 9 H).

Analysis:

Calcd for $C_{18}H_{16}FNO_3$:	C-69.00	H-5.15	N-4.47	F-6.06
Found:	C-68.86	H-5.14	N-4.48	F-6.08

Step B: 3-((S)-Azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 58.0 mL of 1 M potassium bis(trimethylsilyl)amide solution in toluene and 85 mL of THF and was cooled to -78°C. An oven-dried, 250 mL round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 7.20 g (23.0 mmol) of 3-(4-fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone (from Example 58, Step A) in 40 mL of THF. The acyl oxazolidinone solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the potassium bis(trimethylsilyl)amide solution at such a rate that the internal temperature of the mixture was maintained below -70°C. The acyl oxazolidinone flask was rinsed with 15 mL of THF and the rinse was added, via cannula, to the reaction mixture and the resulting mixture was stirred at -78°C for 30 minutes. An oven-dried, 250 mL round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 10.89 g (35.0 mmol) of 2,4,6-triisopropylphenyl-sulfonyl azide in 40 mL of THF. The azide solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the reaction mixture at such a rate that the internal temperature of the mixture was maintained below -70°C. After 2

minutes, the reaction was quenched with 6.0 mL of glacial acetic acid, the cooling bath was removed and the mixture was stirred at room temperature for 18 hours. The quenched reaction mixture was partitioned between 300 mL of ethyl acetate and 300 mL of 50% saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 500 g of silica gel using 2:1 v/v, then 1:1 v/v hexanes/methylene chloride as the eluant afforded 5.45 g (67%) of the title compound as an oil.

IR Spectrum (neat, cm^{-1}): 2104, 1781, 1702.

^1H-NMR (400 MHz, $CDCl_3$): δ 2.86 (dd, 1 H, J = 13.2, 9.6), 3.40 (dd, 1 H, J = 13.2, 3.2), 4.09-4.19 (m, 2 H), 4.62-4.68 (m, 1 H), 6.14 (s, 1 H), 7.07-7.47 (m, 9 H).

Analysis:

Calcd for $C_{18}H_{15}FN_4O_3$: C-61.01 H-4.27 N-15.81 F-5.36

Found: C-60.99 H-4.19 N-15.80 F-5.34

Step C: (S)-Azido-(4-fluorophenyl)acetic acid

A solution of 5.40 g (15.2 mmol) of 3-((S)-azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone (from Example 58, Step B) in 200 mL of 3:1 v/v THF/water was stirred in an ice bath for 10 minutes. 1.28 g (30.4 mmol) of lithium hydroxide monohydrate was added in one portion and the resulting mixture was stirred cold for 30 minutes.

The reaction mixture was partitioned between 100 mL of methylene chloride and 100 mL of 25% saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was washed with 2 x 100 mL of methylene chloride and acidified to pH 2 with 2 N aqueous hydrochloric acid solution. The resulting mixture was extracted with 2 x 100 mL of ethyl acetate; the extracts were combined, washed with 50 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to afford 2.30 g (77%) of the title compound as an oil that was used in the following step without further purification.

IR Spectrum (neat, cm-1): 2111, 1724.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.06 (s, 1 H), 7.08-7.45 (m, 4 H), 8.75 (br s, 1 H).

Step D: (S)-(4-Fluorophenyl)glycine

A mixture of 2.30 g (11.8 mmol) of (S)-azido-(4-fluorophenyl)acetic acid (from Example 58, Step C), 250 mg 10% palladium on carbon catalyst and 160 mL 3:1 v/v water/acetic acid was stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered through Celite and the flask and filter cake were rinsed well with ~1L of 3:1 v/v water/acetic acid. The filtrate was concentrated in vacuo to about 50 mL of volume. 300 mL of toluene was added and the mixture concentrated to afford a solid. The solid was suspended in 1:1 v/v methanol/ether, filtered and dried to afford 1.99 g (100%) of the title compound.

^{1}H-NMR (400 MHz, D_2O + NaOD): δ 3.97 (s, 1 H), 6.77 (app t, 2 H, J = 8.8), 7.01 (app t, 2 H, J = 5.6).

EXAMPLE 59

3-(S)-(4-Fluorophenyl)-4-benzyl-2-morpholinone

Step A: N-Benzyl (S)-(4-fluorophenyl)glycine

A solution of 1.87 g (11.05 mmol) of (S)-(4-fluorophenyl)glycine (from Example 58) and 1.12 mL (11.1 mmol) of benzaldehyde in 11.1 mL of 1 N aqueous sodium hydroxide solution and 11 mL of methanol at 0°C was treated with 165 mg (4.4 mmol) of sodium borohydride. The cooling bath was removed and the resulting mixture was stirred at room temperature for 30 minutes. Second portions of benzaldehyde (1.12 mL (11.1 mmol)) and sodium borohydride 165 mg (4.4 mmol) were added to the reaction mixture and stirring was continued for 1.5 hours. The reaction mixture was partitioned between 100 mL of ether and 50 mL of water and the layers were separated. The aqueous layer was separated and filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 5 with 2 N aqueous hydrochloric acid solution and the solid that had precipitated was filtered, rinsed well with water, then ether, and dried to afford 1.95 g of the title compound.

^{1}H-NMR (400 MHz, D_2O + NaOD): δ 3.33 (AB q, 2 H, J = 8.4), 3.85 (s, 1 H), 6.79-7.16 (m, 4 H).

Step B: 3-(S)-(4-Fluorophenyl)-4-benzyl-2-morpholinone

A mixture of 1.95 g (7.5 mmol) of N-benzyl (S)-(4-fluorophenyl)glycine, 3.90 mL (22.5 mmol) of N,N-diisopropylethylamine, 6.50 mL (75.0 mmol) of 1,2-dibromoethane and 40 mL of N,N-dimethylformamide was stirred at 100°C for 20 hours (dissolution of all solids occurred on warming). The reaction mixture was cooled and concentrated in vacuo. The residue was partitioned between 250 mL of ether and 100 mL of 0.5 N potassium hydrogen sulfate solution and the layers were separated. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate solution, 3 x 150 mL of water, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography on 125 g of silica gel using 3:1 v/v hexanes/ether as the eluant afforded 1.58 g (74%) of the title compound as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.65 (dt, 1 H, J = 3.2, 12.8), 3.00 (dt, 1 H, J = 12.8, 2.8), 3.16 (d, 1 H, J = 13.6), 3.76 (d, 1 H, J = 13.6), 4.24 (s, 1 H), 4.37 (dt, 1 H, J = 13.2, 3.2), 4.54 (dt, 1 H, J = 2.8, 13.2), 7.07-7.56 (m, 9 H).

EXAMPLE 60

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzylmorpholine

The title compound was prepared in 72% yield from 3-(S)-(4-fluorophenyl)-4-benzyl-2-morpholinone

(from Example 59) using procedures analogous to those in Example 15, Steps A and B.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.37 (dt, 1 H, J = 3.6, 11.8), 2.83-2.90 (m, 2 H), 3.55-3.63 (m, 2 H), 3.85 (d, 1 H, J = 13.4), 4.14 (dt, 1 H, J = 2.0, 11.8), 4.44 (d, 1 H, J = 13.6), 4.66 (d, 1 H, J = 2.8), 4.79 (d, 1 H, J = 13.4), 7.00-7.70 (12 H).

EXAMPLE 61

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl) morpholine

The title compound was prepared in 70% yield from 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzylmorpholine (from Example 60) using a procedure analogous to that in Example 15, Step C.

Mass Spectrum (FAB): m/Z 424 (M+H, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.80 (br s, 1 H), 3.11 (app dd, 1 H, J = 2.2, 12.4), 3.25 (dt, 1 H, J = 3.6, 12.4), 3.65 (app dd, 1 H, J = 3.6, 11.4), 4.05 (dt, 1 H, J = 2.2, 11.8), 4.11 (d, 1 H, J = 2.2), 4.53 (d, 1 H, J = 13.6), 4.71 (d, 1 H, J = 2.2), 4.83 (d, 1 H, J = 13.6), 7.04 (t, 2 H, J = 7.2), 7.33-7.37 (m, 2 H), 7.42 (s, 2 H), 7.72 (s, 1 H).

EXAMPLE 62

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl-morpholine

The title compound was prepared in 69% yield from 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)morpholine (from Example 61) using a procedure analogous to that in Example 18.

Mass Spectrum (FAB): m/Z 521 (M+H, 100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.55 (dt, 1 H, J = 3.6, 12.0), 2.91 (d, 1 H, J = 11.6), 2.93 (d, 1 H, J = 14.4), 3.57 (d, 1 H, J = 2.8), 3.59 (d, 1 H, J = 14.4), 3.67-3.70 (m, 1 H), 4.18 (dt, 1 H, J = 2.4, 11.6), 4.48 (d, 1 H, J = 13.6), 4.65 (d, 1 H, J = 2.8), 4.84 (d, 1 H, J = 13.6), 7.07 (t, 2 H, J = 8.4), 7.40 (s, 2 H), 7.45-7.48 (m, 2 H), 7.68 (s, 1 H), 10.04 (br s, 1 H), 10.69 (br s, 1 H).

Analysis:

Calcd for $C_{22}H_{19}F_7N_4O_3$: C-50.78 H-3.68 N-10.77 F-25.55

Found: C-50.89 H-3.76 N-10.62 F-25.56

EXAMPLE 63

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-((3-pyridyl)methyl carbonyl)-3-(R)-phenylmorpholine

A solution of 55 mg (0.315 mmol) of 4-pyridylacetic acid in 1 mL of CH_2Cl_2, containing 0.079 mL (0.715 mmol) of N-methylmorpholine, 53 mg (0.37 mmol) of HOBt and 73 mg (0.37 mmol) of EDC was stirred for 10 min. A solution of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine (from Example 33) in 1 mL of CH_2Cl_2 was added. After stirring the mixture for 2 h, it was partitioned between water and CH_2Cl_2. The organic layer was washed with water, brine and dried by filtering through Na_2SO_4. The filtrate was concentrated and the residue was purified by flash chromatography using 70% EtOAc/hexane to furnish 152 mg (100 % yield) of the product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.0-3.85 (m, 5H), 3.95 & 4.4 (br s, 1H), 4.66 (d, J = 13 Hz, 1H), 4.82 (d, J = 13 Hz, 1H), 5.0 & 5.9 (br s, 1H), 5.23 (s, 1H), 7.1-7.65 (m, 7H), 7.8 (m, 3 H), 8.43 (br s, 2H).

EXAMPLE 64

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-(R)-phenylmorpholine

To a solution of 0.259 g (0.64 mmol) of 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenylmorpholine (from example 33) in 2 mL of DMF were added 0.16 g (0.77 mmol) of methyl 6-bromohexanoate, 0.155 g (1.12 mmol) of K_2CO_3 and 2 crystals of nBu_4NI. The resulting solution was heated in a 60°C bath for 36 h, at which time a tlc indicated incomplete reaction. The bath temperature was raised to 100°C. After 3 h the reaction mixture was cooled and diluted with EtOAc. The EtOAc solution was washed with water (2x), brine and dried over Na_2SO_4. The filtrate was concentrated and the residue was chromatographed using 30% EtOAc/hexane to isolate 220 mg (65%) of the product.

^1H-NMR (400 MHz, $CDCl_3$): δ 1.0-1.4 (m, 4 H), 1.47 (m, J = 8 Hz, 2H), 1.95 (m, 1H), 2.2 (t, J = 8 Hz, 2H), 2.35 (m, 2H), 2.9 (d, J = 13 Hz, 1H), 3.07 (d, J = 7 Hz, 1H), 3.62 (s, 3H), 3.81 (td, J = 8 Hz and 2 Hz, 1 H), 4.04 (dd, J = 10 Hz and 2 Hz, 1H), 4.36 (d, J = 7 Hz, 1H), 4.4 (d, J = 13 Hz, 1H), 4.79 (d, J = 13 Hz, 1H), 7.2-7.4 (m, 7H), 7.66 (s, 1H).

EXAMPLE 65

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(carboxypentyl)-3-(R)-phenylmorpholine

A solution of 0.15 g (0.28 mmol) of 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-(R)-phenylmorpholine (from Example 64) in 3 mL of MeOH was saponified by treating with 0.5 mL of 5 N NaOH for 40 min at 65°C. The solution was cooled, concentrated and the residue was diluted with water. The aqueous solution was adjusted to pH 6 by adding 2 N HCl and it was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The residue upon chromatography on a flash column with 50% EtOAc/hexane furnished 0.13g (89%) of the product

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.0-1.5 (m, 4H), 1.5 (m, 2H), 2.2 (m, 2H), 2.35 (m, 2H), 2.9 (d, J = 13 Hz, 1H), 3.08 (d, J = 7 Hz, 1H), 3.82 (t, J = 8 Hz, 1H), 4.09 (d, J = 7 Hz, 1H), 4.38 (s, 1H), 4.4 (d, J = 13 Hz, 1H), 4.79 (d, J = 13 Hz, 1H), 7.2-7.4 (m, 7H), 7.66 (s, 1H).

EXAMPLE 66

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(methylaminocarbonylpentyl)-6-oxo-hexyl)-3-(R)-phenylmorpholine

A solution of 116 mg (0.22 mmol) of 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-4-(carboxypentyl)-3-(R)-phenylmorpholine (from Example 65) in 1 mL of

CH_2Cl_2 was treated with 40 mg (0.29 mmol) of HOBt, 57 mg (0.29 mmol) of EDC and 0.037 mL of N-methylmorpholine. After 10 min 0.027 mL (0.3 mmol) of aqueous methylamine (40%) was added and the resulting mixture was stirred for 4 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with water, brine and dried over Na_2SO_4, and the filtrate was concentrated. Purification of the residue on a flash column with EtOAc furnished 0.10 g of the product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.0-1.4 (m, 4 H), 1.47 (m, 2H), 1.95 (m, 1H), 2.04 (t, J = 8 Hz, 2H), 2.35 (m, 2H), 2. 74 (d, J = 5 Hz, 3 H), 2.89(d, J =12 Hz, 1H) 3.08 (d, J = 7 Hz, 1H), 3.81 (t, J = 7 Hz, 1H), 4.02 (d, J = 11 Hz, 1H), 4.36 (d, J = 7 Hz, 1H), 4.39 (d, J = 13 Hz, 1H), 4.79 (d, J =13 Hz, 1H), 5.03 (br s, 1H), 7.2-7.4 (m, 7H), 7.65 (s, 1H).

EXAMPLE 67

Typical Pharmaceutical Compositions Containing a Compound of the Invention

A: Dry Filled Capsules Containing 50 mg of Active Ingredient Per Capsule

Ingredient	Amount per capsule (mg)
Active ingredient	50
Lactose	149
Magnesium stearate	1
Capsule (size No. 1)	200

The active ingredient can be reduced to a No. 60 powder and the lactose and magnesium stearate can then be passed through a No. 60 blotting cloth onto the powder. The combined ingredients can then be mixed for about 10 minutes and filled into a No. 1 dry gelatin capsule.

B: Tablet

A typical tablet would contain the active ingredient (25 mg), pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

C: Suppository

Typical suppository formulations for rectal administration contain the active ingredient (0.08-1.0 mg), disodium calcium edetate (0.25-0.5 mg), and polyethylene glycol (775-1600 mg). Other suppository formulations can be made by substituting, for example, butylated hydroxytoluene (0.04-0.08 mg) for the disodium calcium edetate and a hydrogenated vegetable oil (675-1400 mg) such as Suppocire L, Wecobee FS, Wecobee M, Witepsols, and the like, for the polyethylene glycol.

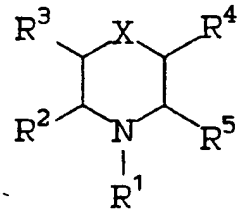
D: Injection

A typical injectible formulation contains the acting ingredient sodium phosphate dibasic anhydrous (11.4 mg), benzyl alcohol (0.01 ml) and water for injection (1.0 ml).

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) hydrogen;

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl,

(iii) hydroxy-C_{1-6} alkyl, and

(iv) phenyl,

(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above,

(m) $-CO_2R^9$, wherein R^9 is as defined above;

(n) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,

(B) benzofuranyl,

(C) benzothiophenyl,

(D) benzoxazolyl,

(E) furanyl,

(F) imidazolyl,

(G) indolyl,

(H) isooxazolyl,

(I) isothiazolyl,

(J) oxadiazolyl,

(K) oxazolyl,

(L) pyrazinyl,

(M) pyrazolyl,

(N) pyridyl,

(O) pyrimidyl,

(P) pyrrolyl,

(Q) quinolyl,

(R) tetrazolyl,

(S) thiadiazolyl,

(T) thiazolyl,

(U) thienyl,
(V) triazolyl,
(W) azetidinyl,
(X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
(AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,

and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) hydroxy,
(v) thioxo,
(vi) $-SR^9$, wherein R^9 is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
(x) trifluoromethyl,
(xi) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and R^9 and R^{10} are as defined above,
(xii) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(xiii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiv) $-CO_2R^9$, wherein R^9 is as defined above, and

(xv) $-(CH_2)_m-OR^9$, wherein m and R^9 are as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,

(i) $-COR^9$ wherein R^9 is as defined above,

(j) $-CO_2R^9$, wherein R^9 is as defined above,

(k) heterocycle, wherein the heterocycle is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,

(b) C_{1-6} alkoxy,

(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;

R^2 and R^3 are independently selected from the group consisting of:
(1) hydrogen,
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy.
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,

(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;

and the groups R^1 and R^2 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,

(e) imidazolyl,
(f) oxazolyl, and
(g) thiazolyl,
and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:
(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a carbocyclic ring selected from the group consisting of:
(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,
and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:
(i) C_{1-6}alkyl,
(ii) C_{1-6}alkoxy,
(iii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

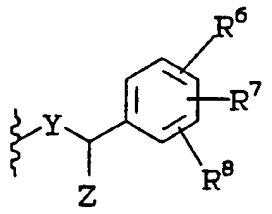
and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

X is selected from the group consisting of:

(1) -O-,
(2) -S-,
(3) -SO-, and
(4) $-SO_2-$;

R^4 is selected from the group consisting of:

(1)  ,

(2) $-Y-C_{1-8}$ alkyl, wherein the alkyl is unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) -Y-C_{2-6} alkenyl, wherein the alkenyl is unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) -O(CO)-phenyl, wherein the phenyl is unsubstituted or substituted with one or more of R^6, R^7 and R^8;

R^5 is selected from the group consisting of:
(1) phenyl, unsubstituted or substituted with one or more of R^{11}, R^{12} and R^{13},
(2) C_{3-7} cycloalkyl,
(3) heterocycle, wherein the heterocycle is as defined above;

R^6, R^7 and R^8 are independently selected from the group consisting of:
(1) hydrogen;
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;
(6) halo,
(7) -CN,
(8) $-CF_3$,
(9) $-NO_2$,
(10) $-SR^{14}$, wherein R^{14} is hydrogen or C_{1-6}alkyl,
(11) $-SOR^{14}$, wherein R^{14} is as defined above,
(12) $-SO_2R^{14}$, wherein R^{14} is as defined above,

(13) NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(14) $CONR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(15) NR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(16) $NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(17) hydroxy,
(18) C_{1-6}alkoxy,
(19) COR^9, wherein R^9 is as defined above,
(20) CO_2R^9, wherein R^9 is as defined above;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8;

Y is selected from the group consisting of:
(1) a single bond,
(2) -O-,
(3) -S-,
(4) -CO-,
(5) $-CH_2-$,
(6) $-CHR^{15}-$, and
(7) $-CR^{15}R^{16}-$, wherein R^{15} and R^{16} are independently selected from the group consisting of:
(a) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(i) hydroxy,
(ii) oxo,
(iii) C_{1-6} alkoxy,

(iv) phenyl-C_{1-3} alkoxy,
(v) phenyl,
(vi) -CN,
(vii) halo,
(viii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(ix) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(x) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(xi) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(xii) $-COR^9$, wherein R^9 is as defined above, and
(xiii) $-CO_2R^9$, wherein R^9 is as defined above;

(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(i) hydroxy,
(ii) C_{1-6} alkoxy,
(iii) C_{1-6} alkyl,
(iv) C_{2-5} alkenyl,
(v) halo,
(vi) -CN,
(vii) $-NO_2$,
(viii) $-CF_3$,
(ix) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(x) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(xi) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(xii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiii) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiv) $-COR^9$, wherein R^9 is as defined above, and

(xv) $-CO_2R^9$, wherein R^9 is as defined above;

Z is selected from:

(1) hydrogen,

(2) C_{1-4} alkyl, and

(3) hydroxy, with the proviso that if Y is -O-, Z is other than hydroxy,

or if Y is $-CHR^{15}-$, then Z and R^{15} may be joined together to form a double bond.

2. The compound of Claim 1 wherein:

R^1 is selected from the group consisting of:

(1) C_{1-6} alkyl, substituted with one or more of the substituents selected from:

(a) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,
(B) imidazolyl,
(C) isooxazolyl,
(D) isothiazolyl,
(E) oxadiazolyl,
(F) pyrazinyl,
(G) pyrazolyl,
(H) pyridyl,
(I) pyrrolyl,
(J) tetrazolyl,
(K) thiadiazolyl,
(L) triazolyl, and
(M) piperidinyl,

and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

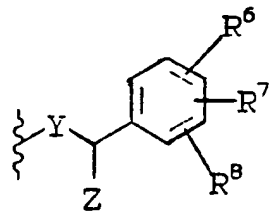
(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) thioxo,
(v) cyano,
(vi) $-SCH_3$,
(vii) phenyl,

(viii) hydroxy,
(ix) trifluoromethyl,
(x) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and wherein R^9 and R^{10} are independently selected from:
(I) hydrogen,
(II) C_{1-6} alkyl,
(III) hydroxy-C_{1-6} alkyl, and
(IV) phenyl,
(xi) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above, and
(xii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above;

R^2 and R^3 are independently selected from the group consisting of:
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) C_{2-6} alkenyl, and
(4) phenyl;

X is -O-;

R^4 is:



,

R^5 is phenyl, unsubstituted or substituted with halo;

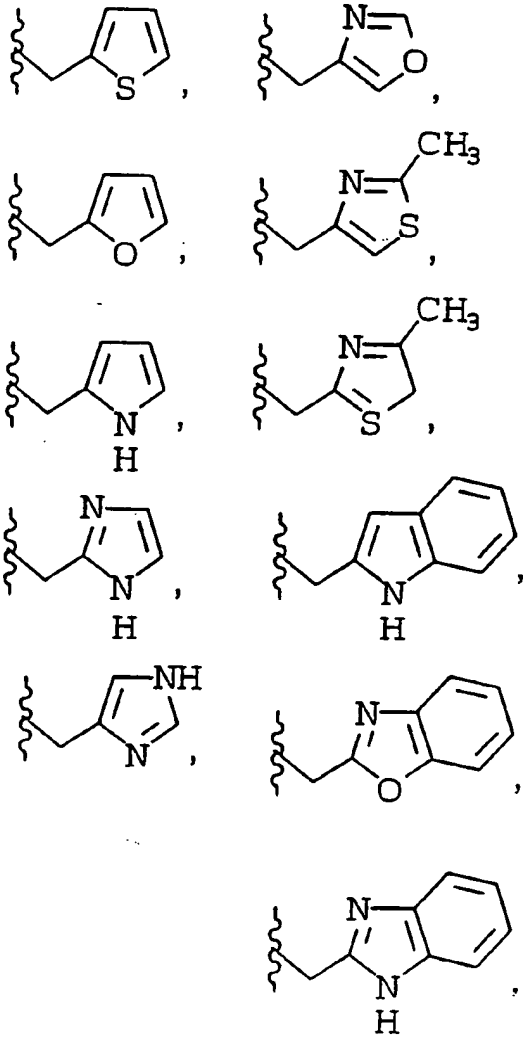
R^6, R^7 and R^8 are independently selected from the group consisting of:

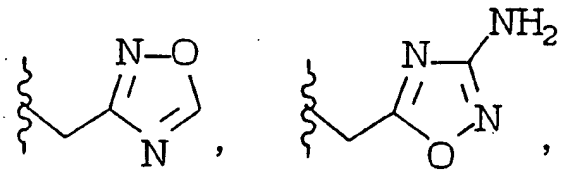
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo, and
(4) $-CF_3$;

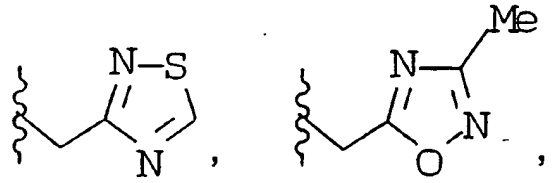
Y is -O-; and

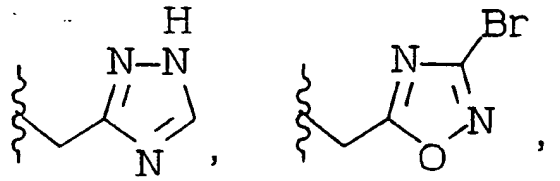
Z is hydrogen or C_{1-4} alkyl.

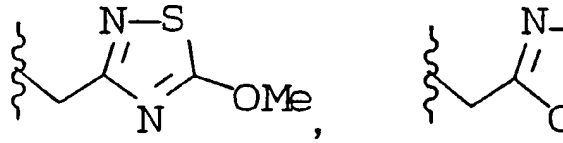
3. The compound of Claim 1 wherein R^1 is selected from the group consisting of:

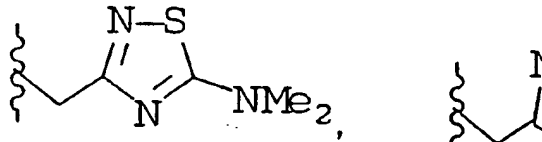


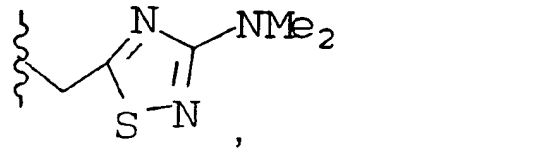


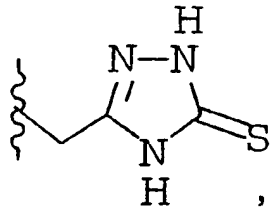








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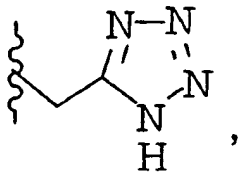
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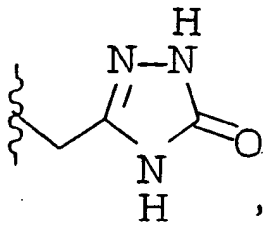
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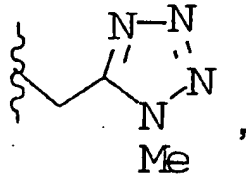
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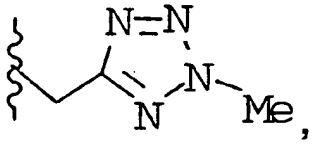
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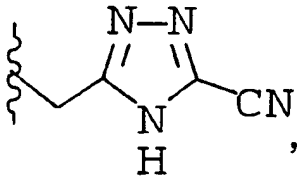
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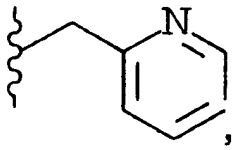
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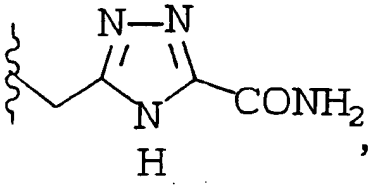
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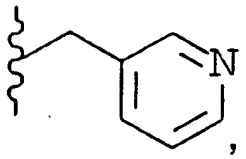
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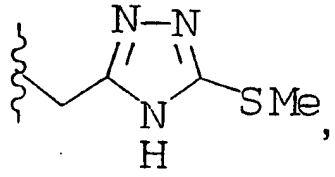
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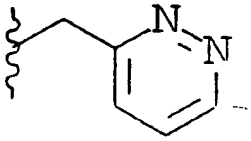
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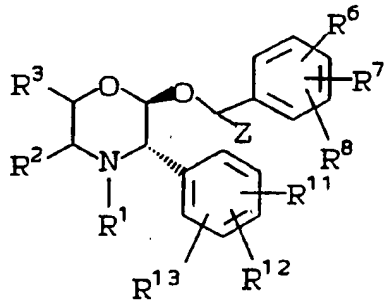
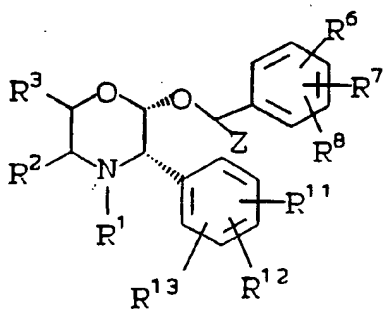
4. The compound of Claim 1 of the structural formula II:



II

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13} and Z are as defined in Claim 1.

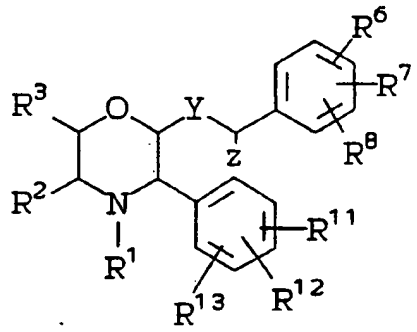
5. The compound of Claim 1 of the structural formula III:



III

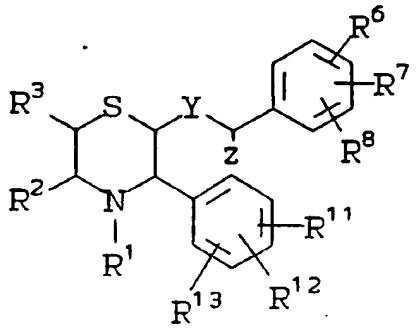
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13} and Z are as defined in Claim 1.

6. The compound of Claim 1 wherein X is O of structural formula:



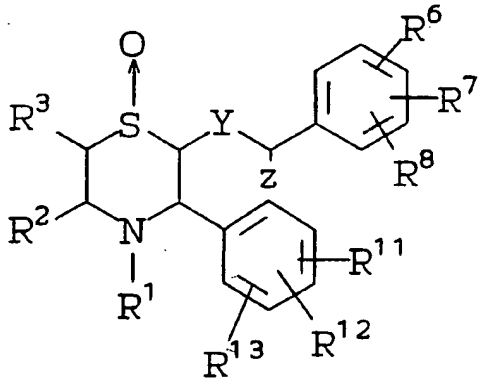
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined in Claim 1.

7. The compound of Claim 1 wherein X is S of structure:



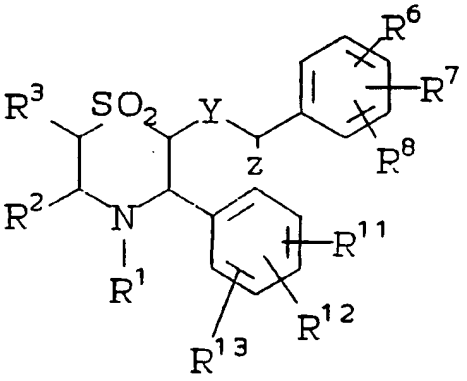
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined in Claim 1.

8. The compound of Claim 1 wherein X is SO of structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined in Claim 1.

9. The compound of Claim 1 wherein X is SO_2 of structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, Y and Z are as defined in Claim 1.

10. A compound which is selected from the group consisting of:

1) 2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

2) (2R,S)-(3,5-bis(trifluoromethyl)benzyloxy)-(3R)-phenyl-(6R)-methyl-morpholine;

3) (2R,S)-(3,5-bis(trifluoromethyl)benzyloxy)-(3S)-phenyl-(6R)-methyl-morpholine;

4) (+/-)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methylcarboxamido-morpholine;

5) (+/-)-2-(3,5-bis(trifluoromethyl)benzyloxy)-3-phenyl-4-methoxy-carbonylmethyl-morpholine;

6) 2-(2-(3,5-bis(trifluoromethyl)phenyl)ethenyl)-3-phenyl-5-oxo-morpholine;

7) 3-phenyl-2-(2-(3,5-bis(trifluoromethyl)phenyl)-ethyl)-morpholine;

8) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl-morpholine;

9) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl-morpholine;

10) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(S)-methyl-morpholine;

11) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(S)-methyl-morpholine;

12) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine;

13) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl-morpholine;

14) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(R)-methyl-morpholine;

15) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-methyl-morpholine;

16) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenylmorpholine;

17) 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

18) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

19) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl-morpholine;

20) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-6-(R)-methyl-morpholine;

21) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;

22) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;

23) 2-(R)-(3,5-bis(trifluoromethyl)-benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine;

24) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(S)-methyl-morpholine;

25) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-methyl-morpholine;

26) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine;

27) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-5-(R)-phenyl-morpholine;

28) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine;

29) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-5-(S)-phenyl-morpholine;

30) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-3-(S)-phenyl-4-(3-(1,2,4-triazolo)methyl)-morpholine;

31) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-6-(R)-methyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;

32) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

33) 4-(3-(1,2,4-triazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

34) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(S)-(3,5-bis-(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

35) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

36) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

37) 4-(aminocarbonylmethyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(R)-phenyl-morpholine;

38) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

39) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-morpholine;

40) 4-(2-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6-(R)-methyl-morpholine;

41) 4-(4-(imidazolo)methyl)-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-6(R)-methyl-morpholine;

42) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((6-hydroxy)hexyl)-3-(R)-phenyl-morpholine;

43) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(5-(methylaminocarbonyl)pentyl)-3-(R)-phenyl-morpholine;

44) 4-(3-(1,2,4-triazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;

45) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3,5-dimethyl)benzyloxy)-3-phenyl-morpholine;

46) 4-(3-(1,2,4-triazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;

47) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3,5-di(tert-butyl)benzyloxy)-3-phenyl-morpholine;

48) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

49) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

50) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(trifluoromethyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

51) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(trifluoromethyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

52) 4-(3-(1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

53) 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

54) 4-(2-(imidazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;

55) 4-(4-(imidazolo)methyl)-2-(3,5-dimethyl-benzyloxy)-3-phenyl-morpholine;

56) 4-(2-(imidazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;

57) 4-(4-(imidazolo)methyl)-2-(3,5-di(tert-butyl)-benzyloxy)-3-phenyl-morpholine;

58) 4-(2-(imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

59) 4-(4-(imidazolo)methyl)-2-(3-(tert-butyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

60) 4-(2-(imidazolo)methyl)-2-(3-(trifluoro-methyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

61) 4-(4-(imidazolo)methyl)-2-(3-(trifluoro-methyl)-5-methylbenzyloxy)-3-phenyl-morpholine;

62) 4-(2-(imidazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

62) 4-(4-(imidazolo)methyl)-2-(3-(tert-butyl)-5-(trifluoromethyl)benzyloxy)-3-phenyl-morpholine;

63) 2-(S)-(3,5-dichlorobenzyloxy)-3-(S)-phenyl-morpholine;

64) 2-(S)-(3,5-dichlorobenzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-3-(S)-phenylmorpholine;

65) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylmethyl)-3-(S)-phenylmorpholine;

66) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxymethyl)-3-(S)-phenylmorpholine;

67) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((2-aminoethyl)aminocarbonylmethyl)-3-(S)-phenyl-morpholine;

68) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((3-aminopropyl)aminocarbonylmethyl)-3-(S)-phenyl-morpholine;

69) 4-benzyl-5-(S),6-(R)-dimethyl-3-(S)-phenylmorpholinone and 4-benzyl-5-(R),6-(S)-dimethyl-3-(S)-phenyl-morpholinone;

70) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(S), 6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone;

71) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-[5-(R), 6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone;

72) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(S),6-(R) or 5-(R), 6-(S)-dimethyl]-3-(S)-phenylmorpholinone;

73) 2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo) methyl)-[5-(S),6-(R) or 5-(R),6-(S)-dimethyl]-3-(S)-phenylmorpholinone;

74) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone;

75) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1,2,4-triazolo)methyl)-[5-(R),6-(S) or 5-(S),6-(R)-dimethyl]-3-(S)-phenylmorpholinone;

76) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(2-(1-(4-benzyl)piperidino)ethyl)-3-(S)-phenyl-morpholine;

77) 3-(S)-(4-fluorophenyl)-4-benzyl-2-morpholinone;

78) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-benzylmorpholine;

79) 2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl) morpholine;

80) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine;

81) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-((3-pyridyl)methyl carbonyl)-3-(R)-phenylmorpholine;

82) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methoxycarbonylpentyl)-3-(R)-phenylmorpholine;

83) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(carboxypentyl)-3-(R)-phenylmorpholine;

84) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(methylaminocarboxypentyl)-6-oxo-hexyl)-3-(R)-phenylmorpholine;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of Claim 1.

12. A method for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a mammal which comprises the administration to the mammal of the compound of Claim 1 in an amount that is effective for antagonizing the effect of substance P at its receptor site in the mammal.

13. A method for antagonizing the effect of neurokinin A at its receptor site or for the blockade of neurokinin-2 receptors in a mammal which comprises the administration to the mammal of the compound of Claim 1 in an amount that is effective for antagonizing the effect of neurokinin A at its receptor site in the mammal.

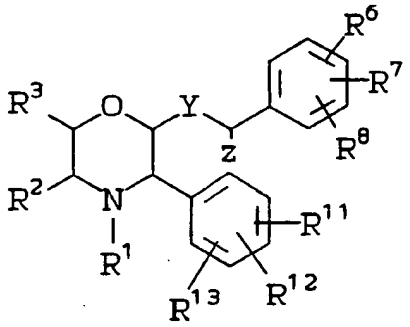
14. A method of treating or preventing pain or nociception attributable to or associated with migraine in a mammal in need thereof which comprises the administration to the mammmal of an effective amount of the compound of Claim 1.

15. A method of treating or preventing a condition selected from the group consisting of: diabetic neuropathy; peripheral neuropathy; AIDS related neuropathy; chemotherapy-induced neuropathy; and neuralgia, in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

16. A method for the treatment or prevention of asthma in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1, either alone or in combination with a neurokinin-2 receptor antagonist or with a β_2-adrenergic receptor agonist.

17. A method for the treatment of cystic fibrosis in a mammal in need thereof which comprises the administration to the mammal of an effective amount of the compound of Claim 1.

18. A process for the preparation of a compound of structural formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) hydrogen;

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,
(ii) C_{1-6} alkyl,
(iii) hydroxy-C_{1-6} alkyl, and
(iv) phenyl,

(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above,

(m) $-CO_2R^9$, wherein R^9 is as defined above;

(n) heterocycle, wherein the heterocycle is selected from the group consisting of:
(A) benzimidazolyl,
(B) benzofuranyl,
(C) benzothiophenyl,
(D) benzoxazolyl,
(E) furanyl,
(F) imidazolyl,
(G) indolyl,
(H) isooxazolyl,
(I) isothiazolyl,
(J) oxadiazolyl,
(K) oxazolyl,
(L) pyrazinyl,
(M) pyrazolyl,
(N) pyridyl,
(O) pyrimidyl,
(P) pyrrolyl,
(Q) quinolyl,
(R) tetrazolyl,
(S) thiadiazolyl,

(T) thiazolyl,
(U) thienyl,
(V) triazolyl,
(W) azetidinyl,
(X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
(AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,
and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) hydroxy,
(v) thioxo,
(vi) $-SR^9$, wherein R^9 is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
(x) trifluoromethyl,
(xi) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and R^9 and R^{10} are as defined above,

(xii) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(xiii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiv) $-CO_2R^9$, wherein R^9 is as defined above, and

(xv) $-(CH_2)_m-OR^9$, wherein m and R^9 are as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above,
(k) heterocycle, wherein the heterocycle is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
- (b) C_{1-6} alkoxy,
- (c) C_{1-6} alkyl,
- (d) C_{2-5} alkenyl,
- (e) halo,
- (f) -CN,
- (g) $-NO_2$,
- (h) $-CF_3$,
- (i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
- (j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
- (k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
- (l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
- (m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
- (n) $-COR^9$, wherein R^9 is as defined above;
- (o) $-CO_2R^9$, wherein R^9 is as defined above;

and the groups R^1 and R^2 may be joined together to form a heterocyclic ring selected from the group consisting of:
- (a) pyrrolidinyl,
- (b) piperidinyl,
- (c) pyrrolyl,
- (d) pyridinyl,

(e) imidazolyl,
(f) oxazolyl, and
(g) thiazolyl,
and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:
(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a carbocyclic ring selected from the group consisting of:
(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,
and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:
(i) C_{1-6}alkyl,
(ii) C_{1-6}alkoxy,
(iii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen;
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,

(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) $-CN$,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;
(6) halo,
(7) $-CN$,
(8) $-CF_3$,
(9) $-NO_2$,

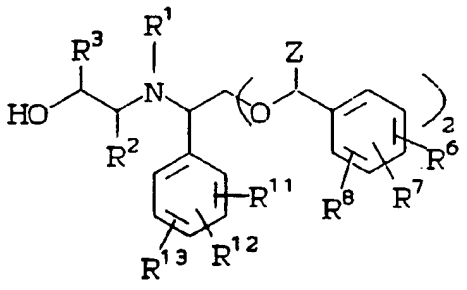
(10) $-SR^{14}$, wherein R^{14} is hydrogen or C_{1-6}alkyl,
(11) $-SOR^{14}$, wherein R^{14} is as defined above,
(12) $-SO_2R^{14}$, wherein R^{14} is as defined above,
(13) NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(14) $CONR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(15) NR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(16) $NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(17) hydroxy,
(18) C_{1-6}alkoxy,
(19) COR^9, wherein R^9 is as defined above,
(20) CO_2R^9, wherein R^9 is as defined above;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8;

Y is -O-;

Z is hydrogen or C_{1-4} alkyl;

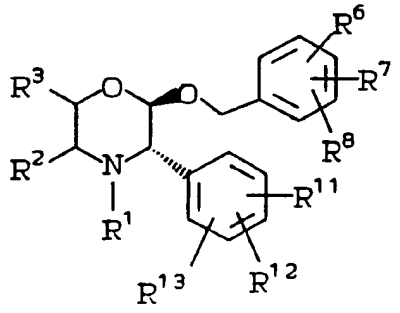
which comprises contacting a compound of formula V:



V

wherein R^1, R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12} and R^{13} are as defined above;
with an inorganic or an organic acid selected from the group consisting of:
toluenesulfonic acid, methanesulfonic acid, sulfuric acid, hydrochloric acid and mixtures thereof,
in an aprotic solvent selected from the group consisting of:
toluene, benzene, dimethylformamide, tetrahydrofuran, diethylether, dimethoxyethane, ethyl acetate, and mixtures thereof,
at a temperature from 0°C to solvent reflux temperature for a sufficient time to produce a compound of structural formula IV.

19. A process for the preparation of a compound of structural formula VI:



VI

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) hydrogen;

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl,

(iii) hydroxy-C_{1-6} alkyl, and

(iv) phenyl,

(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above,

(m) $-CO_2R^9$, wherein R^9 is as defined above;

(n) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,

(B) benzofuranyl,

(C) benzothiophenyl,

(D) benzoxazolyl,
(E) furanyl,
(F) imidazolyl,
(G) indolyl,
(H) isooxazolyl,
(I) isothiazolyl,
(J) oxadiazolyl,
(K) oxazolyl,
(L) pyrazinyl,
(M) pyrazolyl,
(N) pyridyl,
(O) pyrimidyl,
(P) pyrrolyl,
(Q) quinolyl,
(R) tetrazolyl,
(S) thiadiazolyl,
(T) thiazolyl,
(U) thienyl,
(V) triazolyl,
(W) azetidinyl,
(X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
(AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,

and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) hydroxy,
(v) thioxo,
(vi) $-SR^9$, wherein R^9 is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
(x) trifluoromethyl,
(xi) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and R^9 and R^{10} are as defined above,
(xii) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(xiii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(xiv) $-CO_2R^9$, wherein R^9 is as defined above, and
(xv) $-(CH_2)_m-OR^9$, wherein m and R^9 are as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above,
(k) heterocycle, wherein the heterocycle is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;

R^2 and R^3 are independently selected from the group consisting of:
(1) hydrogen,
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
  (a) hydroxy,
  (b) oxo,
  (c) C_{1-6} alkoxy,
  (d) phenyl-C_{1-3} alkoxy,
  (e) phenyl,
  (f) -CN,
  (g) halo,
  (h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
  (i) $-COR^9$ wherein R^9 is as defined above,
  (j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
  (a) hydroxy,
  (b) C_{1-6} alkoxy,
  (c) C_{1-6} alkyl,
  (d) C_{2-5} alkenyl,
  (e) halo,
  (f) -CN,
  (g) $-NO_2$,
  (h) $-CF_3$,
  (i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
  (j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(n) $-COR^9$, wherein R^9 is as defined above;

(o) $-CO_2R^9$, wherein R^9 is as defined above;

and the groups R^1 and R^2 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,

(b) piperidinyl,

(c) pyrrolyl,

(d) pyridinyl,

(e) imidazolyl,

(f) oxazolyl, and

(g) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,

(ii) oxo,

(iii) C_{1-6}alkoxy,

(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(v) halo, and

(vi) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a carbocyclic ring selected from the group consisting of:

(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,

and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:

(i) C_{1-6}alkyl,
(ii) C_{1-6}alkoxy,
(iii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,

(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen;
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
  (a) hydroxy,
  (b) oxo,
  (c) C_{1-6} alkoxy,
  (d) phenyl-C_{1-3} alkoxy,
  (e) phenyl,
  (f) -CN,
  (g) halo,
  (h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
  (i) $-COR^9$ wherein R^9 is as defined above,
  (j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
  (a) hydroxy,
  (b) C_{1-6} alkoxy,
  (c) C_{1-6} alkyl,
  (d) C_{2-5} alkenyl,
  (e) halo,
  (f) -CN,
  (g) $-NO_2$,
  (h) $-CF_3$,
  (i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
  (j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
  (k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(n) $-COR^9$, wherein R^9 is as defined above;

(o) $-CO_2R^9$, wherein R^9 is as defined above;

(6) halo,

(7) -CN,

(8) $-CF_3$,

(9) $-NO_2$,

(10) $-SR^{14}$, wherein R^{14} is hydrogen or C_{1-6}alkyl,

(11) $-SOR^{14}$, wherein R^{14} is as defined above,

(12) $-SO_2R^{14}$, wherein R^{14} is as defined above,

(13) NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,

(14) $CONR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(15) NR^9R^{10}, wherein R^9 and R^{10} are as defined above,

(16) $NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(17) hydroxy,

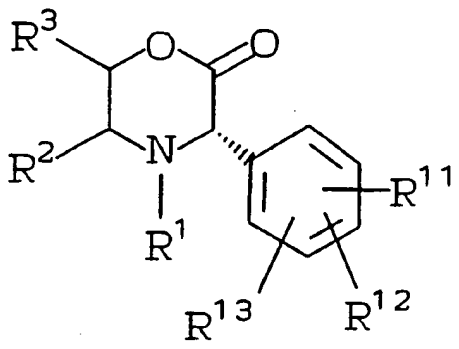
(18) C_{1-6}alkoxy,

(19) COR^9, wherein R^9 is as defined above,

(20) CO_2R^9, wherein R^9 is as defined above;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8;

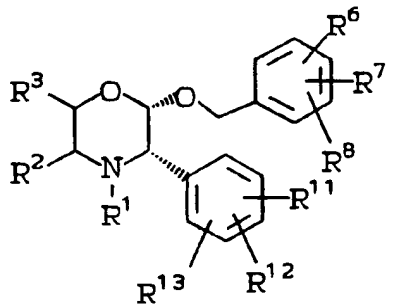
which comprises contacting a compound of formula VII:



VII

wherein R^1, R^2, R^3, R^{11}, R^{12} and R^{13} are as defined above;
with a hydride reducing agent selected from the group consisting of:
diisobutylaluminum hydride, lithium tri(sec-butyl)borohydride, and lithium aluminum hydride,
in an organic solvent at low temperature;
isolating the resultant alcohol;
followed by alkylation of the alcohol with a benzyl halide (in which the phenyl group is substituted with R^6, R^7, and R^8, wherein R^6, R^7, and R^8 are as defined above) in the presence of sodium hydride in an organic solvent for a sufficient time to produce a compound of structural formula VI.

20. A process for the preparation of a compound of structural formula VIII:



VIII

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) hydrogen;

(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,
(ii) C_{1-6} alkyl,
(iii) hydroxy-C_{1-6} alkyl, and
(iv) phenyl,

(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,

(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(l) $-COR^9$, wherein R^9 is as defined above,

(m) $-CO_2R^9$, wherein R^9 is as defined above;

(n) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,
(B) benzofuranyl,
(C) benzothiophenyl,
(D) benzoxazolyl,
(E) furanyl,
(F) imidazolyl,
(G) indolyl,
(H) isooxazolyl,
(I) isothiazolyl,
(J) oxadiazolyl,
(K) oxazolyl,
(L) pyrazinyl,
(M) pyrazolyl,
(N) pyridyl,
(O) pyrimidyl,
(P) pyrrolyl,
(Q) quinolyl,
(R) tetrazolyl,
(S) thiadiazolyl,

(T) thiazolyl,
(U) thienyl,
(V) triazolyl,
(W) azetidinyl,
(X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
(AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,
and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6} alkyl, unsubstituted or substituted with halo, $-CF_3$, $-OCH_3$, or phenyl,
(ii) C_{1-6} alkoxy,
(iii) oxo,
(iv) hydroxy,
(v) thioxo,
(vi) $-SR^9$, wherein R^9 is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
(x) trifluoromethyl,
(xi) $-(CH_2)_m-NR^9R^{10}$, wherein m is 0, 1 or 2, and R^9 and R^{10} are as defined above,

(xii) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,

(xiii) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,

(xiv) $-CO_2R^9$, wherein R^9 is as defined above, and

(xv) $-(CH_2)_m-OR^9$, wherein m and R^9 are as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) -CN,

(g) halo,

(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,

(i) $-COR^9$ wherein R^9 is as defined above,

(j) $-CO_2R^9$, wherein R^9 is as defined above,

(k) heterocycle, wherein the heterocycle is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6} alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,

(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
- (b) C_{1-6} alkoxy,
- (c) C_{1-6} alkyl,
- (d) C_{2-5} alkenyl,
- (e) halo,
- (f) -CN,
- (g) $-NO_2$,
- (h) $-CF_3$,
- (i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
- (j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
- (k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
- (l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
- (m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
- (n) $-COR^9$, wherein R^9 is as defined above;
- (o) $-CO_2R^9$, wherein R^9 is as defined above;

and the groups R^1 and R^2 may be joined together to form a heterocyclic ring selected from the group consisting of:
- (a) pyrrolidinyl,
- (b) piperidinyl,
- (c) pyrrolyl,
- (d) pyridinyl,
- (e) imidazolyl,

(f) oxazolyl, and
(g) thiazolyl,
and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:
(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a carbocyclic ring selected from the group consisting of:
(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,
and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:
(i) C_{1-6}alkyl,
(ii) C_{1-6}alkoxy,
(iii) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R^2 and R^3 may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl,
(ii) oxo,
(iii) C_{1-6}alkoxy,
(iv) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(v) halo, and
(vi) trifluoromethyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen;
(2) C_{1-6}alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(j) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-COR^9$, wherein R^9 is as defined above, and
(m) $-CO_2R^9$, wherein R^9 is as defined above;

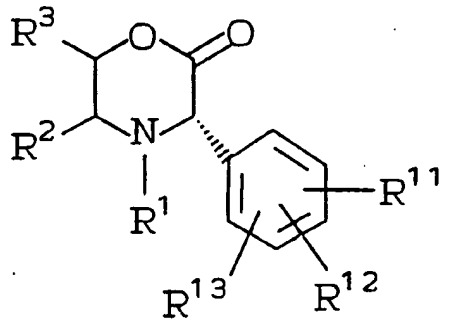
(3) C_{2-6} alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl-C_{1-3} alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) $-CONR^9R^{10}$ wherein R^9 and R^{10} are as defined above,
(i) $-COR^9$ wherein R^9 is as defined above,
(j) $-CO_2R^9$, wherein R^9 is as defined above;

(4) C_{2-6} alkynyl;
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) -CN,
(g) $-NO_2$,
(h) $-CF_3$,
(i) $-(CH_2)_m-NR^9R^{10}$, wherein m, R^9 and R^{10} are as defined above,
(j) $-NR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(k) $-NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(l) $-CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(m) $-CO_2NR^9R^{10}$, wherein R^9 and R^{10} are as defined above,
(n) $-COR^9$, wherein R^9 is as defined above;
(o) $-CO_2R^9$, wherein R^9 is as defined above;
(6) halo,
(7) -CN,
(8) $-CF_3$,
(9) $-NO_2$,
(10) $-SR^{14}$, wherein R^{14} is hydrogen or C_{1-6}alkyl,
(11) $-SOR^{14}$, wherein R^{14} is as defined above,
(12) $-SO_2R^{14}$, wherein R^{14} is as defined above,

(13) NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(14) $CONR^9COR^{10}$, wherein R^9 and R^{10} are as defined above,
(15) NR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(16) $NR^9CO_2R^{10}$, wherein R^9 and R^{10} are as defined above,
(17) hydroxy,
(18) C_{1-6}alkoxy,
(19) COR^9, wherein R^9 is as defined above,
(20) CO_2R^9, wherein R^9 is as defined above;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8;

which comprises contacting a compound of formula IX:



IX

wherein R^1, R^2, R^3, R^{11}, R^{12} and R^{13} are as defined above;
with a hydride reducing agent selected from the group consisting of:

diisobutylaluminum hydride, lithium tri(sec-butyl)borohydride, and lithium aluminum hydride;

in an organic solvent at low temperature;
followed by alkylation of the resultant alcohol/alkoxide with a phenylmethyl-leaving group reagent (in which the phenyl group is substituted with R^6, R^7, and R^8, wherein R^6, R^7, and R^8 are as defined above and wherein the leaving group is selected from triflate, mesylate, tosylate, p-nitrophenylsulfonate, bromo and iodo) in an organic solvent at low temperature for a sufficient time to produce a compound of structural formula VIII.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/06181

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D265/32; C07D265/30; C07D279/12; C07D413/06
A61K31/535

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 436 334 (PFIZER INC.) 10 July 1991 cited in the application see claims	1-20
A	FR,A,2 534 915 (LABORATOIRE L. LAFON) 27 April 1984 see claims	1-20
P,A	EP,A,0 528 495 (MERCK SHARP & DOHME LTD.) 24 February 1993 see claims	1-20

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 OCTOBER 1993	12. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	CHOULY J.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/06181

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-17 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9306181
SA 76421

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 05/10/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0436334	10-07-91	WO-A- 9109844	11-07-91
		EP-A- 0558156	01-09-93
FR-A-2534915	27-04-84	None	
EP-A-0528495	24-02-93	AU-A- 2413892	16-03-93
		WO-A- 9304040	04-03-93